

08/624,508

From the INTERNATIONAL BUREAU

**PCT**NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

SAMA, Daniele  
Sama Patents  
Via Masera, 10  
I-20129 Milano  
ITALIEDate of mailing 02 April 1996  
(day/month/year) (02.04.96)

Applicant's or agent's file reference

94113B99

## IMPORTANT NOTIFICATION

International application No.

PCT/EP94/03182

International filing date 23 September 1994  
(day/month/year) (23.09.94)

## 1. The following indications appeared on record concerning:



the applicant



the inventor



the agent



the common representative

Name and Address

NICOX LIMITED  
17 Dame Street  
Dublin 2  
Ireland

State of Nationality

IE

State of Residence

IE

Telephone No.

Facsimile No.

Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:



the person



the name



the address



the nationality



the residence

Name and Address

NICOX S.A.  
45 Avenue Kléber  
F-75116 Paris  
France

State of Nationality

FR

State of Residence

FR

Telephone No.

Facsimile No.

Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:



the receiving Office



the designated Offices concerned



the International Searching Authority



the elected Offices concerned



the International Preliminary Examining Authority



other:

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

G. Bähr

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 730.91.11

## PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

**PCT****NOTIFICATION OF THE RECORDING  
OF A CHANGE**(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

SAMA, Daniele  
Sama Patents  
Via Masera, 10  
I-20129 Milano  
ITALIEDate of mailing 24 May 1995 (24.05.95)  
(day/month/year)Applicant's or agent's file reference  
94113B99**IMPORTANT NOTIFICATION**International application No.  
PCT/EP94/03182International filing date  
(day/month/year) 23 September 1994  
(23.09.94)

## 1. The following indications appeared on record concerning:

☐

the applicant

☐

the inventor

☒

the agent

☐

the common representative

## Name and Address

TRUPIANO, Roberto  
Brevetti Europa S.r.l.  
Piazza Bernini, 6  
I-20133 Milano  
ITALY

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

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the person

☒

the name

☒

the address

☐

the nationality

☐

the residence

## Name and Address

SAMA, Daniele  
Sama Patents  
Via Masera, 10  
I-20129 Milano  
ITALY

State of Nationality

State of Residence

Telephone No.

2-29521908

Facsimile No.

2-29521926

Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

☒

the receiving Office

☐

the designated Offices concerned

☐

the International Searching Authority

☒

the elected Offices concerned

☒

the International Preliminary Examining Authority

☐

other:

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

J. Leita

Facsimile No. (41-22) 740.14.35

Telephone No. (41 22) 730.91.11

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Washington D.C. 20231  
United States of America

in its capacity as elected Office

Date of mailing:

24 May 1995 (24.05.95)

International application No.:

PCT/EP94/03182

Applicant's or agent's file reference:

94113B99

International filing date:

23 September 1994 (23.09.94)

Priority date:

06 October 1993 (06.10.93)

Applicant:

DEL SOLDATO, Piero

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

25 April 1995 (25.04.95)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Leitao

Telephone No.: (41-22) 730.91.11

## PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING  
DOCUMENT TRANSMITTED

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Washington D.C. 20231  
United States of America

in its capacity as elected Office

Date of mailing (day/month/year)

19 January 1996 (19.01.96)

International application No.

PCT/EP94/03182

International filing date (day/month/year)

23 September 1994 (23.09.94)

Applicant

NICOX LIMITED et al

The International Bureau transmits herewith the following documents and number thereof:

\_\_\_\_\_ copy of the international preliminary examination report and annexes (Article 36(3)(a))

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

K. Andreasson

Telephone No.: (41-22) 730.91.11

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>94113B99</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 94/03182</b>	International filing date( <i>day/month/year</i> ) <b>23/09/94</b>	(Earliest) Priority Date ( <i>day/month/year</i> ) <b>06/10/93</b>
Applicant <b>NICOX LIMITED et al.</b>		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
  - ☐ filed with the international application.
  - ☐ furnished by the applicant separately from the international application,
    - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
  - ☐ Transcribed by this Authority
4. With regard to the title, ☒ the text is approved as submitted by the applicant.
  - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
  - ☒ the text is approved as submitted by the applicant.
  - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
  - Figure No.            ☐ as suggested by the applicant. ☐ None of the figures.
  - ☐ because the applicant failed to suggest a figure.
  - ☐ because this figure better characterizes the invention.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 94/03182

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C203/04 C07D487/04 C07D209/28 A61K31/40 A61K31/405  
A61K31/21 //(C07D487/04, 209:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,17 93 828 (SYNTEX CORP.) 22 April 1976 see the whole document & ZA,A,6 707 597 (...) cited in the application ---	1-18
A	DE,A,14 43 429 (BOOTS PURE DRUG COMPANY LTD.) 24 October 1968 see the whole document & GB,A,971 700 (...) cited in the application ---	1-18
A	US,A,3 758 544 (SYNTEX CORP.) 11 September 1973 see abstract; claims & DE,A,19 34 460 (...) 23 June 1977 cited in the application ---	1-18
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance  
"E" earlier document but published on or after the international filing date  
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
"O" document referring to an oral disclosure, use, exhibition or other means  
"P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
"&" document member of the same patent family

Date of the actual completion of the international search

14 December 1994

Date of mailing of the international search report

- 4. 01. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Paisdor, B

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,28 14 556 (SANKYO CO., LTD.) 12 October 1978 cited in the application see claims ---	1-18
P,A	WO,A,94 12463 (HCT-HEALTH CARE TRADING LTD.) 9 June 1994 see abstract; claims ---	1-18
P,A	WO,A,94 04484 (CORLAY S.L. & METGROVE LTD.) 3 March 1994 see abstract; claims -----	1-18

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 94/03182

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-1793828	22-04-76	DE-A, B, C 1793825	05-02-76
		CA-A- 960689	07-01-75
		CA-A- 991655	22-06-76
		CH-A- 517690	15-01-72
		CH-A- 520644	31-03-72
		CH-A- 520645	31-03-72
		CH-A- 537369	13-07-73
		DE-A- 1668654	15-04-71
		FR-M- 8487	27-07-73
		FR-M- 8494	27-07-73
		FR-A- 1587861	03-04-70
		GB-A- 1211134	04-11-70
		NL-A- 7512107	30-01-76
		NL-A- 6800251	15-07-68
		US-A- 3896157	22-07-75
		US-A- 3904682	09-09-75
		US-A- 4048330	13-09-77
		US-A- 4207241	10-06-80
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ZA-A-6707597		NONE	
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DE-A-1443429	24-10-68	FR-M- 3124	
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		US-A- 3385886	
		US-A- 3385887	
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GB-A-971700		DE-A, B, C 1443429	24-10-68
		FR-M- 3124	
		US-A- 3228831	
		US-A- 3385886	
		US-A- 3385887	
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US-A-3758544	11-09-73	US-A- 3873594	25-03-75
		CH-A- 554306	30-09-74
		CH-A- 554826	15-10-74
		CH-A- 535735	15-04-73
		DE-A- 1934460	05-02-70
		GB-A- 1274271	17-05-72
		GB-A- 1274272	17-05-72



## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 94/03182

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3758544		GB-A- 1274273	17-05-72
		NL-A- 6911574	03-02-70
		SE-C- 392263	21-03-77
		US-A- 3637767	25-01-72
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DE-A-1934460	05-02-70	CH-A- 554306	30-09-74
		CH-A- 554826	15-10-74
		CH-A- 535735	15-04-73
		GB-A- 1274271	17-05-72
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		SE-C- 392263	21-03-77
		US-A- 3637767	25-01-72
		US-A- 3758544	11-09-73
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DE-A-2814556	12-10-78	JP-C- 1173362	28-10-83
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		JP-B- 58004699	27-01-83
		JP-C- 1310718	11-04-86
		JP-A- 53127444	07-11-78
		JP-B- 60034539	09-08-85
		JP-C- 1310723	11-04-86
		JP-A- 54016458	07-02-79
		JP-B- 60034540	09-08-85
		BE-A- 869097	18-01-79
		CA-A- 1113113	24-11-81
		CH-A- 633515	15-12-82
		FR-A, B 2395256	19-01-79
		GB-A- 1580113	26-11-80
		NL-A, B, C 7803644	09-10-78
		SE-B- 437261	18-02-85
		SE-A- 7803848	06-10-78
		US-A- 4161538	17-07-79
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WO-A-9412463	09-06-94	AU-B- 5624194	22-06-94
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WO-A-9404484	03-03-94	CA-A- 2120942	03-03-94
		EP-A- 0609415	10-08-94
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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 94/03182

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C203/04 C07D487/04 C07D209/28 A61K31/40 A61K31/405  
A61K31/21 //(C07D487/04,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,17 93 828 (SYNTEX CORP.) 22 April 1976 see the whole document & ZA,A,6 707 597 (...) cited in the application ---	1-18
A	DE,A,14 43 429 (BOOTS PURE DRUG COMPANY LTD.) 24 October 1968 see the whole document & GB,A,971 700 (...) cited in the application ---	1-18
A	US,A,3 758 544 (SYNTEX CORP.) 11 September 1973 see abstract; claims & DE,A,19 34 460 (...) 23 June 1977 cited in the application --- -/--	1-18

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

14 December 1994

Date of mailing of the international search report

- 4. 01. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Paisdor, B

# INTERNATIONAL SEARCH REPORT

Int. l. Application No  
PCT/EP 94/03182

## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,28 14 556 (SANKYO CO., LTD.) 12 October 1978 cited in the application see claims ---	1-18
P,A	WO,A,94 12463 (HCT-HEALTH CARE TRADING LTD.) 9 June 1994 see abstract; claims ---	1-18
P,A	WO,A,94 04484 (CORLAY S.L. & METGROVE LTD.) 3 March 1994 see abstract; claims -----	1-18

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

PCT/EP 94/03182

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-1793828	22-04-76	DE-A, B, C 1793825	05-02-76
		CA-A- 960689	07-01-75
		CA-A- 991655	22-06-76
		CH-A- 517690	15-01-72
		CH-A- 520644	31-03-72
		CH-A- 520645	31-03-72
		CH-A- 537369	13-07-73
		DE-A- 1668654	15-04-71
		FR-M- 8487	27-07-73
		FR-M- 8494	27-07-73
		FR-A- 1587861	03-04-70
		GB-A- 1211134	04-11-70
		NL-A- 7512107	30-01-76
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		US-A- 3904682	09-09-75
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		US-A- 3385887	
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GB-A-971700		DE-A, B, C 1443429	24-10-68
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		US-A- 3385887	
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US-A-3758544	11-09-73	US-A- 3873594	25-03-75
		CH-A- 554306	30-09-74
		CH-A- 554826	15-10-74
		CH-A- 535735	15-04-73
		DE-A- 1934460	05-02-70
		GB-A- 1274271	17-05-72
		GB-A- 1274272	17-05-72

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

PCT/EP 94/03182

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3758544		GB-A- 1274273	17-05-72
		NL-A- 6911574	03-02-70
		SE-C- 392263	21-03-77
		US-A- 3637767	25-01-72
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DE-A-1934460	05-02-70	CH-A- 554306	30-09-74
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		US-A- 3637767	25-01-72
		US-A- 3758544	11-09-73
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DE-A-2814556	12-10-78	JP-C- 1173362	28-10-83
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		JP-C- 1310718	11-04-86
		JP-A- 53127444	07-11-78
		JP-B- 60034539	09-08-85
		JP-C- 1310723	11-04-86
		JP-A- 54016458	07-02-79
		JP-B- 60034540	09-08-85
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		CA-A- 1113113	24-11-81
		CH-A- 633515	15-12-82
		FR-A,B 2395256	19-01-79
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WO-A-9412463	09-06-94	AU-B- 5624194	22-06-94
<hr/>			
WO-A-9404484	03-03-94	CA-A- 2120942	03-03-94
		EP-A- 0609415	10-08-94
<hr/>			

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

19  
REC'D 17 JAN 1996


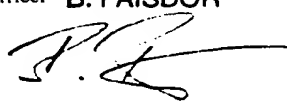
Applicant's or agent's file reference <b>HF 9428+9429</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/EP 94/ 03182</b>	International filing date ( <i>day/month/year</i> ) <b>23/09/1994</b>	Priority date ( <i>day/month/year</i> ) <b>06/10/1993</b>
International Patent Classification (IPC) or national classification and IPC <b>C07C203/04</b>		
Applicant <b>NICOX LIMITED et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of 2 sheets.

3. This report contains indications and corresponding pages relating to the following items:
  - I ☒ Basis of the report
  - II ☐ Priority
  - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☒ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand <b>25/04/1995</b>	Date of completion of this report <b>16.01.96</b>
Name and mailing address of the IPEA  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <b>B. PAISDOR</b>  Telephone No.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

EP94/03182

## I. Basis of the report

1. This report has been drawn up on the basis of:

☐ the international application as originally filed

☒ the description, pages 1 - 18, 20 - 31 as originally filed  
 pages filed with the demand  
 page 19, filed with the letter of 10.10.95

☒ the Claims No. 1 - 9, 14 (part), 15 - 18 as originally filed  
 No. as amended under Article 19  
 No. filed with the demand  
 No. 10 - 14 (part), filed with the letter of 10.10.95

☐ the drawings, sheets / fig. as originally filed  
 sheets / fig. filed with the demand  
 sheets / fig. filed with the letter of

2. The amendments have resulted in the cancellation of:

☐ pages:

☐ Claims No.

☐ drawings, sheets / fig.

3. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 c)).

4. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty	Claims	1 - 18	YES
Inventive Step	Claims	1 - 18	YES
Industrial Applicability	Claims	1 - 10, 15 - 18	YES
	Claims	11 - 14	SEE BELOW

**2. Citations and Explanations**

2.1 The following documents have been considered for the purposes of this report:

D1 WO,A,94/12463  
D2 WO,A,94/04484  
D3 DE,A,2814556

2.2 Novelty (Article 33(2) PCT)

2.2.1 In document D3 substituted phenylacetic acid derivatives having anti-inflammatory activity is disclosed. The compounds of formula (I) of D3 can be compared with the structurally closely related compounds of the present claim 1, in which the group M of formula (IA) is represented by a group (XXXIII) wherein the substituent R is a group (X). In contrast to D3 the compounds of claim 1 of the present application are either esters or amides containing a nitric ester functional group of these acetic acid derivatives. Therefore claim 1 of this application represents novel subject-matter.

2.2.2 Consequently, the other independent (use) claims 11 - 14, the claims 15 and 16 pertaining to processes for the preparation of compounds of the principal claim, the claims 17 and 18 for pharmaceutical compositions containing the compounds of claim 1 and the remaining dependent claims 2 - 10 are also novel in the sense of Article 33(2) PCT.

2.3 Inventive Step (Article 33(3) PCT)



2.3.1 Document D3, which is considered to represent the most relevant state of the art, discloses (cf., e.g. page 23, table) substituted phenylacetic acid and phenylpropionic acid derivatives having anti-inflammatory and analgetic activity from which the subject-matter of claim 1 differs only in that it pertains to nitric esters of amide and/or ester derivatives of formula (IA). To show this distinguishing structural feature, example 1 of D3 (cf. page 24) can be compared with a compound according to claim 1 in which the groups A and B are hydrogen, n is 1, Y is oxygen and M represents a group (XXXIII) in which R represents a group (X).

2.3.2 The technical problem to be solved by the present invention may therefore be regarded as to provide **further** phenylpropionic and/or phenylacetic acid derivatives having anti-inflammatory and analgesic activity.

2.3.3 Nowhere in the prior art documents being currently on file an indication for a person skilled in the art can be found that nitric ester derivatives of the phenylpropionic acid compounds (for example) known from D3 might also possess the same pharmacological activities. Therefore an inventive step in the sense of Article 33(3) PCT is acknowledged for the compounds of claim 1.

2.3.4. Consequently, the claims 2 - 10 depending on claim 1 and the remaining independent claims 11 - 18 which refer to the preparation, and the application of the novel and inventive compounds according to claim 1 also represent inventive subject-matter.

2.4 For the assessment of the present claims 11 - 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

## VI. Certain documents cited

## 1. Certain published documents (Rule 70.10)

Application no. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO,A,94/12463	09/06/94	15/11/93	26/11/92
WO,A,94/04484	03/03/94	20/06/93	20/08/92

These documents **could** be relevant for the assessment of inventive step of the present application (cf. Rule 64(3) PCT).

WO,A,94/12463 (D1) discloses nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity; the groups Y, A and B of the compounds of general formula (I) (cf. D1, page 3) are the same as in this application. The meaning of the numeral n is identical and the substituent R<sup>2</sup> can be hydrogen or methyl as in the compounds of formula (IA) of the present claim 1. The distinguishing structural feature consists in the group R of D1 as can be shown by comparing, e.g. compound (XVIII) (cf. page 18 of D1) with example 1 of this application (cf. formula (IV), page 19).

In WO,A,94/04484 (D2) nitric esters of 2-(2,6-di-halophenylamino)phenylacetic acid also having, e.g. anti-inflammatory activity are disclosed. Again, the groups Y, A, B and the numeral n of D2 have the same meaning as in the present application. The comparison of e.g. compound (II) (cf. page 9, D2) with a compound according to claim 1 in which the group M represents a group (XXXI) and Y, A, B and n are the same as in formula (IV) (cf. page 19) shows that the distinguishing structural feature consists in the dihalophenylaminophenyl group of D2.

# PATENT COOPERATION TREATY

## PCT

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:  
SAMA, Daniele  
SAMA PATENTS  
Via Masera, 10  
I-20129 Milano  
ITALIE

SAMA PATENTS

22 GEN 1996

RECEIVED

NOTIFICATION OF TRANSMITTAL OF  
INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year)

16. 01. 96

### IMPORTANT NOTIFICATION

Applicant's or agent's file reference  
HF 9428+9429

International application No.  
PCT/EP 94/ 03182

International filing date (day/month/year)  
23/09/1994

Priority date (day/month/year)  
06/10/1993

Applicant

NICOX LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA



European Patent Office, P.B. 5818 Patentaan 2  
NL-2280 HV Rijswijk - Netherlands  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
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Authorized officer

E. Reisinger

Telephone No.

E. Reisinger

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)


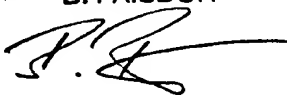
Applicant's or agent's file reference <b>HF 9428+9429</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/EP 94/ 03182</b>	International filing date ( <i>day/month/year</i> ) <b>23/09/1994</b>	Priority date ( <i>day/month/year</i> ) <b>06/10/1993</b>
International Patent Classification (IPC) or national classification and IPC <b>C07C203/04</b>		
Applicant <b>NICOX LIMITED et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of 5 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of 2 sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand <b>25/04/1995</b>	Date of completion of this report <b>16. 01. 96</b>
Name and mailing address of the IPEA  European Patent Office, P.B. 5818 Patendaan 2 NL-2280 HV Rijswijk - Netherlands Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <b>B. PAISDOR</b>  Telephone No.

## I. Basis of the report

1. This report has been drawn up on the basis of:

☐ the international application as originally filed

☒ the description. pages 1 - 18, 20 - 31 as originally filed  
pages filed with the demand  
page 19 . filed with the letter of 10.10.95

☒ the Claims No. 1 - 9, 14 (part), 15 - 18 as originally filed  
No. as amended under Article 19  
No. . filed with the demand  
No. 10 - 14 (part) . filed with the letter of 10.10.95

☐ the drawings. sheets / fig. as originally filed  
sheets / fig. . filed with the demand  
sheets / fig. . filed with the letter of

2. The amendments have resulted in the cancellation of:

☐ pages:☐ Claims No.☐ drawings. sheets / fig.3. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 c)).

4. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty	Claims	1 - 18	YES
Inventive Step	Claims	1 - 18	YES
Industrial Applicability	Claims	1 - 10, 15 - 18	YES
	Claims	11 - 14	SEE BELOW

**2. Citations and Explanations**

**2.1** The following documents have been considered for the purposes of this report:

D1 WO,A,94/12463  
D2 WO,A,94/04484  
D3 DE,A,2814556

**2.2 Novelty (Article 33(2) PCT)**

**2.2.1** In document D3 substituted phenylacetic acid derivatives having anti-inflammatory activity is disclosed. The compounds of formula (I) of D3 can be compared with the structurally closely related compounds of the present claim 1, in which the group M of formula (IA) is represented by a group (XXXIII) wherein the substituent R is a group (X). In contrast to D3 the compounds of claim 1 of the present application are either esters or amides containing a nitric ester functional group of these acetic acid derivatives. Therefore claim 1 of this application represents novel subject-matter.

**2.2.2** Consequently, the other independent (use) claims 11 - 14, the claims 15 and 16 pertaining to processes for the preparation of compounds of the principal claim, the claims 17 and 18 for pharmaceutical compositions containing the compounds of claim 1 and the remaining dependent claims 2 - 10 are also novel in the sense of Article 33(2) PCT.

**2.3 Inventive Step (Article 33(3) PCT)**

2.3.1 Document D3, which is considered to represent the most relevant state of the art, discloses (cf., e.g. page 23, table) substituted phenylacetic acid and phenylpropionic acid derivatives having anti-inflammatory and analgetic activity from which the subject-matter of claim 1 differs only in that it pertains to nitric esters of amide and/or ester derivatives of formula (IA). To show this distinguishing structural feature, example 1 of D3 (cf. page 24) can be compared with a compound according to claim 1 in which the groups A and B are hydrogen, n is 1, Y is oxygen and M represents a group (XXXIII) in which R represents a group (X).

2.3.2 The technical problem to be solved by the present invention may therefore be regarded as to provide **further** phenylpropionic and/or phenylacetic acid derivatives having anti-inflammatory and analgesic activity.

2.3.3 Nowhere in the prior art documents being currently on file an indication for a person skilled in the art can be found that nitric ester derivatives of the phenylpropionic acid compounds (for example) known from D3 might also possess the same pharmacological activities. Therefore an inventive step in the sense of Article 33(3) PCT is acknowledged for the compounds of claim 1.

2.3.4. Consequently, the claims 2 - 10 depending on claim 1 and the remaining independent claims 11 - 18 which refer to the preparation, and the application of the novel and inventive compounds according to claim 1 also represent inventive subject-matter.

2.4 For the assessment of the present claims 11 - 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

EP94/03182

## VI. Certain documents cited

### 1. Certain published documents (Rule 70.10)

Application no. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO,A,94/12463	09/06/94	15/11/93	26/11/92
WO,A,94/04484	03/03/94	20/06/93	20/08/92

These documents **could** be relevant for the assessment of inventive step of the present application (cf. Rule 64(3) PCT).

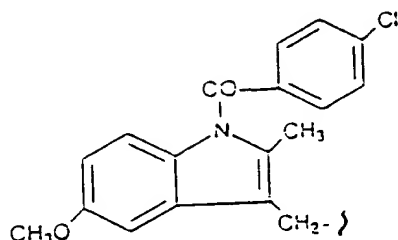
WO,A,94/12463 (D1) discloses nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity; the groups Y, A and B of the compounds of general formula (I) (cf. D1, page 3) are the same as in this application. The meaning of the numeral n is identical and the substituent R<sup>2</sup> can be hydrogen or methyl as in the compounds of formula (IA) of the present claim 1. The distinguishing structural feature consists in the group R of D1 as can be shown by comparing, e.g. compound (XVIII) (cf. page 18 of D1) with example 1 of this application (cf. formula (IV), page 19).

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n is equal to four.

10. Derivatives of 1-(p- chlorobenzoyl) -5-methoxy - 2-methyl-3-indolylacetic acid according to claim 1, characterized in that M is equal to



(XXXII)

A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

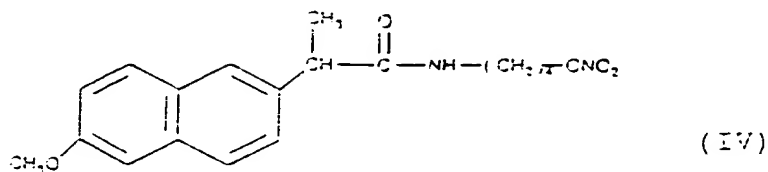
The use of  
11. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~  
~~in the pharmaceutical field~~  
as anti-inflammatory agents.

The use of  
12. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~  
~~in the pharmaceutical field~~  
as analgesic agents.

The use of  
13. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~  
~~in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.~~

The use of  
14. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~  
~~in the treatment of the diseases of the cardiovascular system, in the treatment~~

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



which is prepared as described in the following example, that is given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

#### EXAMPLE 2

a) 23.9 g of potassium-phthalimide dispersed into 200 ml of anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by distillation at the pressure of <sup>1.33 KPa</sup> (10 mm Hg.)

The residue was regained with water and extracted with methylene chloride.

AMENDED SHEET  
IPEA/EP

## INTERNATIONAL SEARCH REPORT

Int. Application No  
CT/EP 94/03182

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C203/04 C07D487/04 C07D209/28 A61K31/40 A61K31/405  
A61K31/21 //(C07D487/04,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,17 93 828 (SYNTEX CORP.) 22 April 1976 see the whole document & ZA,A,6 707 597 (...) cited in the application ---	1-18
A	DE,A,14 43 429 (BOOTS PURE DRUG COMPANY LTD.) 24 October 1968 see the whole document & GB,A,971 700 (...) cited in the application ---	1-18
A	US,A,3 758 544 (SYNTEX CORP.) 11 September 1973 see abstract; claims & DE,A,19 34 460 (...) 23 June 1977 cited in the application ---	1-18
-/-		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

14 December 1994

Date of mailing of the international search report

- 4. 01. 95

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Paisdor, B

## INTERNATIONAL SEARCH REPORT

Int. Application No.  
PCT/EP 94/03182

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,28 14 556 (SANKYO CO., LTD.) 12 October 1978 cited in the application see claims ---	1-18
P,A	WO,A,94 12463 (HCT-HEALTH CARE TRADING LTD.) 9 June 1994 see abstract; claims ---	1-18
P,A	WO,A,94 04484 (CORLAY S.L. & METGROVE LTD.) 3 March 1994 see abstract; claims -----	1-18

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 94/03182

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-1793828	22-04-76	DE-A, B, C 1793825	05-02-76
		CA-A- 960689	07-01-75
		CA-A- 991655	22-06-76
		CH-A- 517690	15-01-72
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		DE-A- 1668654	15-04-71
		FR-M- 8487	27-07-73
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		FR-A- 1587861	03-04-70
		GB-A- 1211134	04-11-70
		NL-A- 7512107	30-01-76
		NL-A- 6800251	15-07-68
		US-A- 3896157	22-07-75
		US-A- 3904682	09-09-75
		US-A- 4048330	13-09-77
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ZA-A-6707597		NONE	
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		GB-A- 971700	
		US-A- 3228831	
		US-A- 3385886	
		US-A- 3385887	
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GB-A-971700		DE-A, B, C 1443429	24-10-68
		FR-M- 3124	
		US-A- 3228831	
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US-A-3758544	11-09-73	US-A- 3873594	25-03-75
		CH-A- 554306	30-09-74
		CH-A- 554826	15-10-74
		CH-A- 535735	15-04-73
		DE-A- 1934460	05-02-70
		GB-A- 1274271	17-05-72
		GB-A- 1274272	17-05-72

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3758544		GB-A- 1274273 NL-A- 6911574 SE-C- 392263 US-A- 3637767	17-05-72 03-02-70 21-03-77 25-01-72
DE-A-1934460	05-02-70	CH-A- 554306 CH-A- 554826 CH-A- 535735 GB-A- 1274271 GB-A- 1274272 GB-A- 1274273 NL-A- 6911574 SE-C- 392263 US-A- 3637767 US-A- 3758544	30-09-74 15-10-74 15-04-73 17-05-72 17-05-72 17-05-72 03-02-70 21-03-77 25-01-72 11-09-73
DE-A-2814556	12-10-78	JP-C- 1173362 JP-A- 53135958 JP-B- 58004699 JP-C- 1310718 JP-A- 53127444 JP-B- 60034539 JP-C- 1310723 JP-A- 54016458 JP-B- 60034540 BE-A- 869097 CA-A- 1113113 CH-A- 633515 FR-A,B 2395256 GB-A- 1580113 NL-A,B,C 7803644 SE-B- 437261 SE-A- 7803848 US-A- 4161538	28-10-83 28-11-78 27-01-83 11-04-86 07-11-78 09-08-85 11-04-86 07-02-79 09-08-85 18-01-79 24-11-81 15-12-82 19-01-79 26-11-80 09-10-78 18-02-85 06-10-78 17-07-79
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WO-A-9404484	03-03-94	CA-A- 2120942 EP-A- 0609415	03-03-94 10-08-94



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07C 203/04, C07D 487/04, 209/28,</b> <b>A61K 31/40, 31/405, 31/21 // (C07D</b> <b>487/04, 209:00, 209:00)</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/09831</b> <b>(43) International Publication Date:</b> <b>13 April 1995 (13.04.95)</b>
<b>(21) International Application Number:</b> <b>PCT/EP94/03182</b> <b>(22) International Filing Date:</b> <b>23 September 1994 (23.09.94)</b> <b>(30) Priority Data:</b> <div style="display: flex; justify-content: space-between;"> <div> <b>9320599.5</b>  <b>MI94/A000916</b> </div> <div> <b>6 October 1993 (06.10.93)</b>  <b>10 May 1994 (10.05.94)</b> </div> <div> <b>GB</b>  <b>IT</b> </div> </div> <b>(71) Applicant (for all designated States except US):</b> <b>NICOX LIMITED [IE/IE]; 17 Dame Street, Dublin 2 (IE).</b> <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> <b>DEL SOLDATO, Piero [IT/IT]; Via E. Toti, 22, I-20052 Monza (IT).</b> <b>(74) Agent:</b> <b>TRUPIANO, Roberto; Brevetti Europa S.r.l., Piazza Bernini, 6, I-20133 Milano MI (IT).</b>		<b>(81) Designated States:</b> <b>AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).</b>  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> <b>NITRIC ESTERS HAVING ANTI-INFLAMMATORY AND/OR ANALGESIC ACTIVITY AND PROCESS FOR THEIR PREPARATION</b>  <div style="text-align: center; margin: 20px 0;"> <math display="block">\text{M}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Y}-(\overset{\text{A}}{\underset{\text{B}}{\text{C}}})_n-\text{ONO}_2 \quad (\text{IA})</math> </div> <b>(57) Abstract</b>  <p>The present invention refers to nitric esters of derivatives of propionic acid, 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid, 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, 6-methoxy-2-naphthylacetic acid, having general formula (IA), their pharmaceutical use and the process for their preparation.</p>		

NITRIC ESTERS HAVING ANTI-INFLAMMATORY AND/OR ANALGESIC  
ACTIVITY AND PROCESS FOR THEIR PREPARATION.

#### OBJECT OF THE INVENTION

The present invention refers to nitric esters of derivatives of propionic acid, 1-(p-chlorobenzoyl)-5-methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl-1,2-dihydro -3H- pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid, their pharmaceutical utilization and the process for their preparation. The present invention also refers to pharmaceutical compositions comprising at least one of said nitric esters as active constituent.

#### PRIOR ART

Some derivatives of propionic acid, such as, for instance, 2-(6-methoxy-2-naphtyl)propionic acid 2-(4-isobutylphenyl)propionic acid or alpha-Methyl-4-[(2-oxocyclopentyl)methyl]benzeneacetic acid, have been used for a long time in the pharmaceutical field for their anti-inflammatory activity and have been present for many years on the different world markets. The process for the preparation of 2-(6-methoxy-2-naphtyl)propionic acid has been described in the South African Patent N°6707,597, in the German Patent N°1,934,460, corresponding to the US Patent N°3,637,767 and also in C.A.71,91162j (1969); HARRISON et al. J.Med.Chem. 13,203 (1970); the process for the preparation of 2-(4-isobutylphenyl)propionic acid has been



described in Patents GB N°971,700, US N°3,228,831 and  
US N°3,385,886, and also in T. SHIORI, N. KAWAI, J.Org.  
Chem. 43,2936 (1978); J.T. PINHEY, B.A. ROWE, Tetrahe-  
dron Letters 21, 965 (1980); while the process for the  
5 preparation of alpha-methyl-4-[(2-oxocyclopentyl)meth-  
yl]benzenacetic acid has been described in the German  
Patent N°2,814,556 and in US Patent N°4,161,538.

In the case of 2-(6-methoxy-2-naphtyl)propionic acid,  
the pharmacological profile is described in ROSZKOWSKI  
10 et al. J. Pharmacol. Exp. Ther. 179,114 (1971), while  
the pharmacological profile of 2-(4-  
isobutylphenyl)propionic acid is reported in ADAMS et  
al. Arch. Pharmacodyn. Ther. 178,115 (1969).

The utilization of these derivatives of propionic acid  
15 as anti-inflammatory agents involves, as known, extre-  
mely severe adverse reactions affecting, for instance,  
the gastrointestinal system, as well as damages to  
liver and kidneys.

Other particularly toxic products are, for example, 5-  
20 benzoyl -,2- dihydro-3H- pyrrolo[1,2-a] pyrrole 1-  
carboxylic acid or Ketorolac [W.H.ROOKS et al. Agents  
Actions 12,684 (1982)] and 1-(4-chlorobenzoyl)-5-  
methoxy-2- methyl- 1H-indole- 3-acetic acid or Indomet-  
hacin [C.D.KLAASSEN, Toxicol. Appl. Pharmacol. 28,127  
25 (1976)]. In particular, in some countries Ketorolac has  
been withdrawn from the market because of its gastroin-  
testinal toxicity, while Indomethacin is one of the

drugs which has caused the highest death-rate from the year of its introduction in the market. Compared with other known anti-inflammatory and/or analgesic drugs, Ketorolac and Indomethacin cause - because of the already described adverse reactions - very extensive damages and, in particular as concerns gastrointestinal toxicity, deaths have been ascertained even in children.

It is therefore evident that there is the need of having drugs which, though providing a good anti-inflammatory and/or analgesic activity, do not result to be, in general, toxic.

#### OBJECTS OF THE INVENTION

Object of the present invention is that of providing a product which, while assuring at least the maintenance of the pharmacological activity which is characteristic of the known anti-inflammatory and/or analgesic agents, is capable of eliminating the adverse reactions brought about by the treatment with said agents, and has good tolerance.

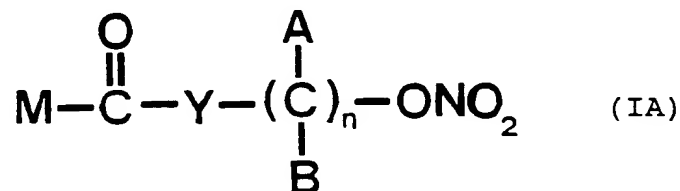
Another object of the present invention is that of realizing a process for the preparation of derivatives of propionic acid, 1-(p-chlorobenzoyl)-5-methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl -1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole -1-carboxylic acid, 6-methoxy -2-naphthylacetic acid, having an anti-inflammatory and/or analgesic activity, good tolerance and being

exempt from the adverse reactions that are typical of anti-inflammatory and analgesic agents.

Still another object of the present invention is that of providing pharmaceutical compositions having anti-inflammatory and/or analgesic activity which results provided with good tolerance.

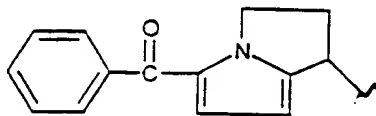
#### DESCRIPTION OF THE INVENTION

These and still further objects and associated advantages which shall clearly result from the following description, are reached by derivatives of propionic acid, 1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid, 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid, 6-methoxy-2-naphthylacetic acid which, according to the present invention, have the following general formula:

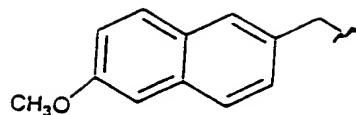


where:

A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, M is chosen among:

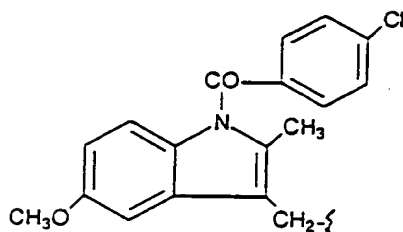


(XXX)



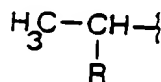
(XXXI)

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(XXXII)

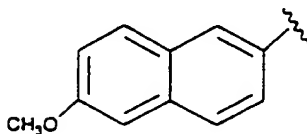
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(XXXIII)

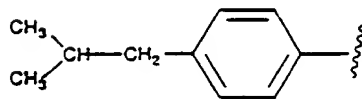
where R is chosen among:

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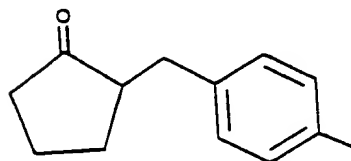


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(III)



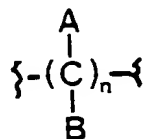
(X)

25

Y is chosen among oxygen, NH, NR<sub>1</sub>, where R<sub>1</sub> is a linear

or branched alkyl group, and n is comprised between 1 and 10.

More particularly, the fragment



is a linear, branched or cyclic alkylenic group  $\text{C}_2\text{-C}_{10}$ . In fact, it has been observed that the introduction of a group such as a terminal nitric ester in the derivatives (IA) permits to maintain the pharmacological activity which is characteristic of anti-inflammatory non steroidal and/or analgesic agents, leads to products provided with good tolerance, while eliminating the adverse reactions caused by the treatment with such drugs. Furthermore, the introduction of a terminal nitric ester in the derivatives of propionic acid, permits to potentiate the anti-inflammatory effect compared with the well known non-steroidal anti-inflammatory drugs; such increase is made by the terminal nitric ester group, which can be considered as a source of nitric oxide and which can exert additional anti-inflammatory effects.

It has been also observed that the derivatives (IA) are useful in the treatment of different unhealthy conditions, for instance unhealthy conditions which required the treatment with both anti-inflammatory and analgesic drug, or rheumatic diseases in general, disorders of an

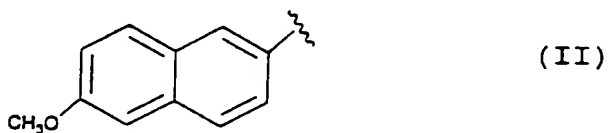
immunologic nature, and they can also alleviate moderate-medium painful states of any kind.

Moreover, the derivatives (IA) subject matter of this invention, are useful in the treatment of the illnesses of the cardiovascular system and of the central nervous system, in particular in the treatment of myocardial and brain ischaemiae, as well as in some cases of arterial thrombosis and in some cases of senile dementia.

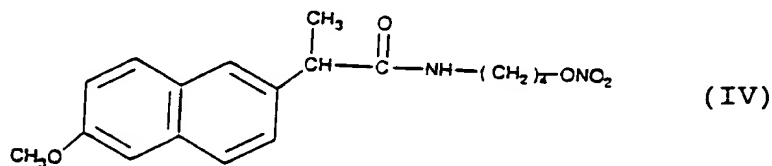
Always according to this invention, a nitric ester (IA) proved to be particularly advantageous, where: hydrogen is chosen as A and B, M is chosen as



where R is chosen as:



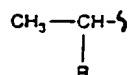
NH is chosen as Y, and n is equal to four, according to the following formula:



A nitric ester (IA) has also proved to be particularly advantageous according to this invention, where:

hydrogen is chosen as A and B, M is chosen as

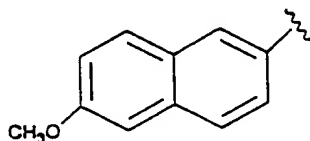
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(XXXIII)

where R is chosen as:

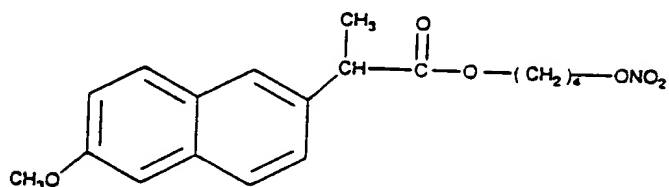
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(II)

oxygen is chosen as Y, an n is equal to four, according to the following formula:

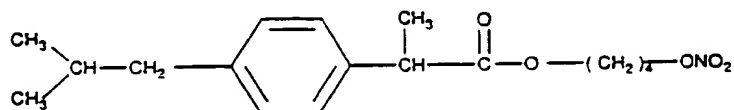
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(V)

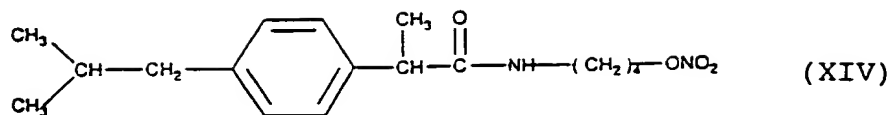
20 Also the nitric esters of derivatives of 2-(4-isobutylphenyl)propionic acid have proved to be particularly advantageous according to this invention, having the following formulae:

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(XIII)

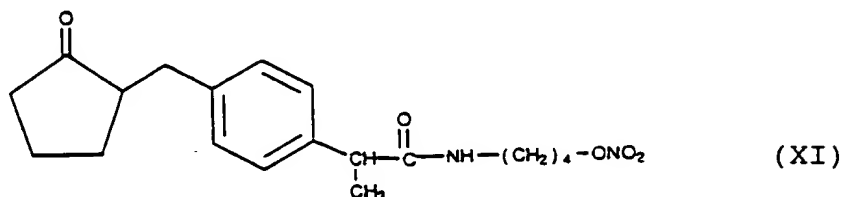
and



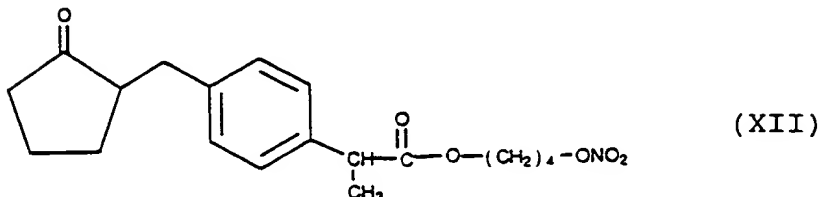
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Always according to the present invention, nitric esters (IA) have proved to be particularly advantageous, having the following formulae:

10

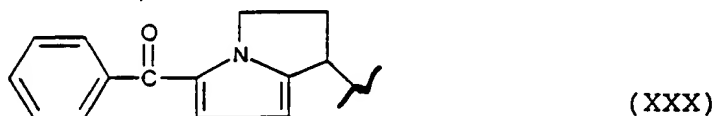


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Always according to the present invention, nitric esters (IA) where M is chosen as

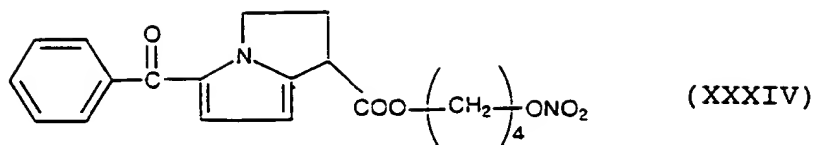


25

oxygen is chosen as Y, hydrogen is chosen as A and B and n is equal to four according to the following



formula:



5

proved to have very good tolerance.

For the preparation of nitric esters (IA) subject matter of the present invention, a first process has proved to be particularly advantageous which, according to the present invention, includes the following steps:

10

- Preparation of sodium salt of derivatives having the following general formula:



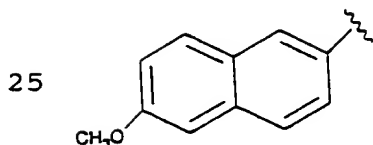
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where M is chosen among (XXX), (XXXI), (XXXII),



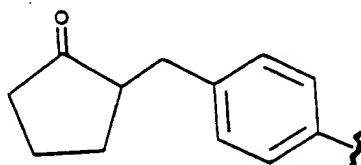
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where R is chosen among the following structures:

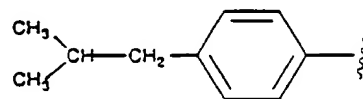


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(II)



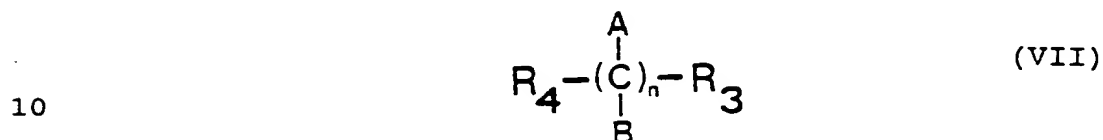
(X)



(III)

or preparation of derivatives (VIA) functionalized to the carboxylic group as acyclic chlorides, anhydrides or the like;

- 5 - Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a composition having the following general formula:



where:

15  $\text{R}_4$  is chosen among chlorine, bromine,  $\text{NHR}_5$  with  $\text{R}_5$  hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substitutes alkyl chains,  $\text{R}_3$  is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- 20 - Reaction of said monomeric esters or said amides with a nitrating agent such as  $\text{AgNO}_3$  or the like, with ensuing production of nitric esters (IA).

A second process has also proved to be particularly advantageous which, always according to the present invention, includes the following steps:

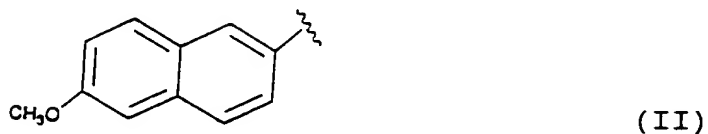
- 25 - Preparation of sodium salt of derivatives having the following general formula:



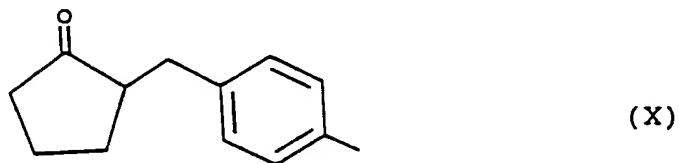
5 where M is chosen among (XXX), (XXXI), (XXXII),



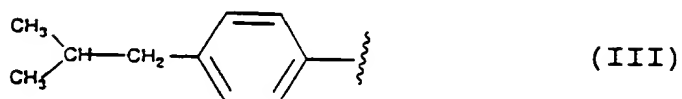
10 where R is chosen among the following structures:



15



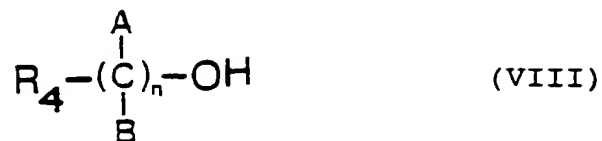
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25 or preparation of derivatives (VIA) functionalized to the carboxylic group, such as acyclic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a composition having the

following general formula:



5

where;

R<sub>4</sub> is chosen among chlorine, bromine, NHR<sub>5</sub> with R<sub>5</sub> hydrogen, linear or branched alkyl chains, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

10

- Reaction of said monomeric esters or said amides with an halogenating composition such as PBr<sub>3</sub> or the like, with ensuing prouction of said monomeric esters or said amides characterized by the presence of a terminal halogen group;

15

- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group, with a nitrating agent such as AgNO<sub>3</sub> or the like, with ensuing production of nitric esters of derivatives (IA).

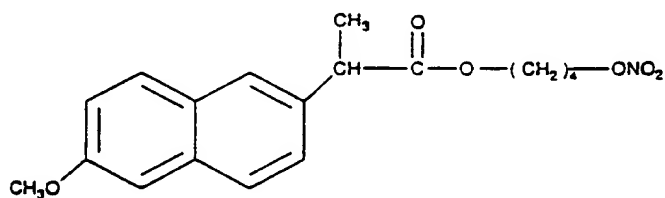
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The solvents which are utilized in the processes subject matter of the present invention are preferably chosen among chloroform, methylene chloride, acetonitrile, dimethylformamide, tetrahydrofuran, 1,4-dioxane and the like.

25

Such processes for the preparation of derivatives (IA), subject matter of the present invention, consist of a limited number of steps, which permits to obtain in a short time the products which derive from these processes, with satisfactory yields and in high amounts, also on the industrial level.

According to the processes subject matter of this invention, the preparation of a nitric ester derived from propionic acid has proved to be particularly advantageous, having the following formula:



(V)

which is prepared as described in the example that is given hereunder as a mere indication and which does not limit in any way the protection scope of the invention.

#### EXAMPLE 1

a) 0.59 g of EtONa dissolved in 10 ml of ethyl alcohol were added, by slow dripping, to a solution of 2 g of 2-(6-methoxy-2-naphtyl)propionic acid, dissolved in 20 ml of ethyl alcohol. The reaction mixture was stirred for 5 minutes at room temperature, then the solvent was evaporated at a reduced pressure, obtaining 2.1 g of sodium salt of 2-(6-methoxy-2-naphtyl)propionic acid. The 2.1 g of sodium salt of 2-(6-methoxy-2-naphtyl)

propionic acid so obtained were dispersed in 40 ml of dimethylformamide and 1.5 g of 1-Br-4-Cl-butane dissolved in 30 ml of dimethylformamide were added by dripping to this dispersion. The reaction mixture was stirred for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The organic phase so extracted was anhydriified on sodium sulfate and the solvent was evaporated at a reduced pressure until a dry residue of 2 g was obtained.

The residue was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v).

The head fractions were collected, the solvent was evaporated at a reduced pressure and 1 g of 2-(6-methoxy-2-naphtyl)propionate of 4-chlorobutyl (IX) was obtained.

IR( $\text{cm}^{-1}$ ): C=O, 1669.

$^1\text{H-NMR}$ (300MHz) ( $\text{CDCl}_3$ ): 1.6ppm (d, 3H); 1.75ppm (m, 4H); 3.45ppm (m, 2H); 3.88ppm (q, 1H); 3.91ppm (t, 3H); 4.1ppm (m, 2H); 7.1-7-7.7ppm (m, aromatics).

Mass spectrometry (i.e.):  $\text{M}^+$  320.

b) 0.79 g of  $\text{AgNO}_3$  dissolved in 1.3 ml of acetonitrile were dripped to 1 g of (IX) obtained as described in a), dissolved in 4,5 ml of acetonitrile. The reaction mixture was stirred for 12 hours at a temperature of 85°C and then filtered.

From the resulting solution, the solvent was evaporated

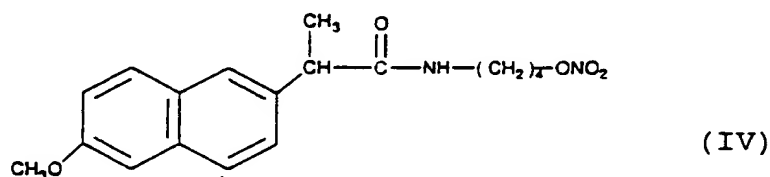
at a reduced pressure, and a residue was obtained to which 10 ml of methylene chloride were added. The mix so obtained was filtered once again, the organic phase was washed with water and then anhydriified on sodium sulfate. The solvent was evaporated under reduced pressure and 1.8 g of a dry residue was obtained, which was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v). The fractions containing the product were collected, the solvent was evaporated at a reduced pressure and 1.5 g of nitric ester of 2-(6-methoxy-2-naphthyl)propionate of 4-hydroxy-butyl (V) were obtained.

IR( $\text{cm}^{-1}$ ): C=O, 1733;  $\text{ONO}_2$ , 1637.

$^1\text{H-NMR}$ (300MHz) ( $\text{CDCl}_3$ ): 1.6ppm (d, 3H); 1.65ppm (m, 4H); 3.8ppm (q, 1H); 3.9ppm (s, 3H); 4.1ppm (m, 2H); 4.3ppm (m, 2H); 7.1-7.7ppm (m, aromatics).

Mass spectrometry (i.e.)  $\text{M}^+$  347.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



which is prepared as described in the following example, that is given hereunder as a mere indication and

which does not limit in any way the protection scope of this invention.

EXAMPLE 2

5 a) 23.9 g of potassium-phthalimide dispersed into 200 ml of anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

10 The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by distillation at the pressure of 10 mm Hg.

15 The residue was regained with water and extracted with methylene chloride.

The organic phase so obtained was anhydriified and the solvent was evaporated at a reduced pressure until 14.8 g of 1-phthalimide-4-bromo-butane were obtained, which were treated with isopropyl ether and then essiccated.

20 m.p. = 77°C

b) 32 ml of hydriodic acid were cautiously added to 8.25 g of 1-phthalimido-4-bromo-butane; the mixture was then submitted to heating and kept in ebullition for 24 hours.

25 After cooling, the mixture was diluted with water and after filtration the solvent was evaporated at a reduced pressure, obtaining a residue which, once crystal-



lized by ethyl ether, produced 6 g of 4-iodine-butylammonium iodide.

m.p. = 103°C

5 c) 7 ml of thionyl chloride were cautiously added to a solution of 2.3 g of 2-(6-methoxy-2-naphtyl)propionic acid in 15 ml of anhydrous chloroform. The reaction mixture was stirred for 40 minutes at room temperature and then the solvent was evaporated at a reduced pressure, obtaining 2.23 g of 2-(6-methoxy-2-naphtyl)propionylchloride.

2.3 g of 2-(6-methoxy-2-naphtyl)propionylchloride were dissolved in pyridine and the solution was cooled at the temperature of 0°C.

15 3.27 g of 4-iodobutylammonium iodide were added to this solution and the mixture so obtained was agitated for 1 hour at 0°C and then diluted with water and extracted with methylene chloride.

20 The organic phase so obtained was washed initially with a 10% solution of hydrochloric acid and afterward with a saturated solution of sodium bicarbonate, then the solvent was evaporated at a reduced pressure, obtaining 3.2 g of a dry residue. The residue was purified by chromatography on silica gel, utilizing methylene chloride as eluent.

25 The intermediate fractions were collected, the solvent was evaporated at a reduced pressure and 1.6 g of 2-(6-methoxy-2-naphtyl)-4-iodobutyl propionamide (XX) were

obtained.

IR ( $\text{cm}^{-1}$ ): NH, 3294; C=O, 1651.

$^1\text{H-NMR}$ (300MHz) ( $\text{CDCl}_3$ ): 1.1-1.75 ppm (m, 4H);

1.6ppm (d, 3H); 3.1ppm (t, 2H); 3.2ppm (q, 2H); 3.7ppm  
5 (q, 1H); 3.9ppm (s, 3H); 5.35ppm (m, NH); 7.1-7.75ppm  
(m, aromatics).

d) A suspension of 1.6 g of 2-(6-methoxy-2-naphtyl)-4-  
iodobutyl propionamide in 20 ml of acetonitrile was  
heated at a temperature of about 40°C and stirred until  
10 a solution was obtained to which 1.0 g of  $\text{AgNO}_3$  were  
added.

The mixture was stirred for 1 hour at room temperature,  
then filtered and the solvent was evaporated at a  
reduced pressure. The residue obtained was regained  
15 with methylene chloride, the resulting mixture was  
filtered and the solvent was evaporated at a reduced  
pressure, and 0,8 g of dry residue were obtained which  
were purified by chromatography on silica gel, utili-  
zing an eluting mixture constituted by methylene chlo-  
20 ride/ethyl acetate 9/1 (v/v).

The head fractions were collected, the solvent was  
evaporated at a reduced pressure and 0.75 g of nitric  
ester of 2-(6-methoxy-2-naphtyl)-4-hydroxybutyl propio-  
namide (IV) were obtained.

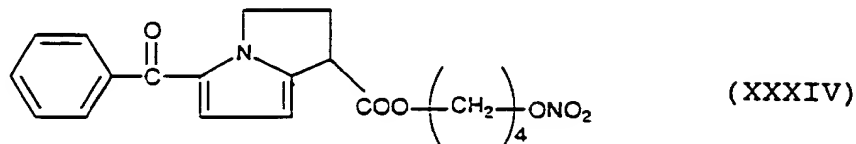
25 IR( $\text{cm}^{-1}$ ): C=O, 1672; NH, 3294;  $\text{ONO}_2$ , 1637

Mass spectrometry (i.e.)  $\text{M}^+$  346.

$^1\text{H-NMR}$ (80mhz) ( $\text{CDCl}_3$ ): 1.3ppm-1.6ppm (m, 4H);

1.7ppm (d, 3H); 3.1ppm (q, 2H); 3.7ppm (q, 1H); 3.9ppm (s, 3H); 4.3ppm (m, 2H); 5.6ppm (m, NH); 7.05-7.8ppm (m, aromatics).

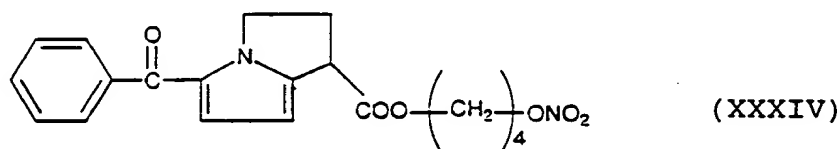
Always according to the present invention, also the  
5 nitric ester having the following formula:



10 proved to be particularly advantageous, which is prepared as described in the following example that is also given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.  
15

### EXAMPLE 3

Preparation of the composition having the formula:

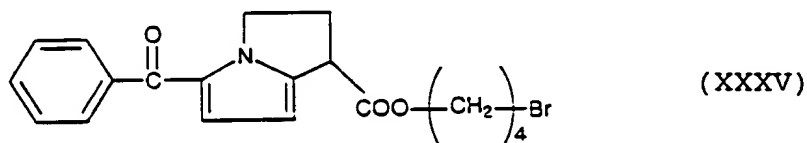


20 a) In a suspension of 80% sodium hydride (0,16 g) in DMF (15 ml), 1,15 g of Ketorolac dissolved in 20 ml of DMF were caused to drip under agitation.  
25

The reaction mix was kept under agitation at 40°C for

15 minutes, then 1 ml of 1,4-dibromobutane was added and the mix was kept under agitation at room temperature overnight.

Then the solvent was evaporated under reduced pressure and the residue was treated with water and methylene chloride. The organic phase was separated, dried on sodium sulfate and the solvent was removed under reduced pressure, to obtain a residue which was purified by silica gel chromatography, utilizing a 4/6 petroleum ether/ether eluent mix (v/v). The head fractions were collected, the solvent was evaporated under reduced pressure and 0.75 g of product was obtained having the formula:



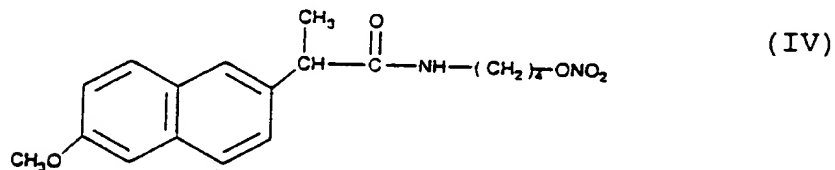
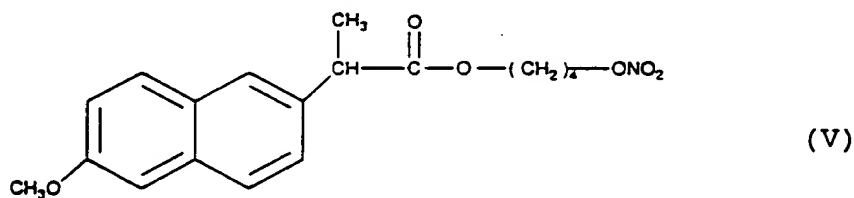
<sup>1</sup>H-NMR (80 MHz) (CDCl<sub>3</sub>) (ppm): 1,83(6H, m); 2,81(2H, m); 3,38(2H, t); 4,12(2H, t); 4,48(1H, m); 6,03(1H, d); 6,78(1H, d); 7,41(3H, m); 7,73(2H, m).

b) A solution of AgNO<sub>3</sub> (0,5 g) in 5 ml of acetonitrile was added to a solution of (XXXV) (0,75 g) in 20 ml of acetonitrile. The reaction mix was kept stirring at room temperature for 48 hours. The solvent was then removed under pressure and the residue was treated with water and methylene chloride. The organic phase

was then separated, dried on sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by filtration on silica gel, utilizing a 4/6 petroleum ether/ether eluent mix. The head fractions were collected, the solvent was evaporated under reduced pressure and 0.35 g of (XXXIV) were obtained.

$^1\text{H-NMR}$  (80 MHz) ( $\text{CDCl}_3$ ) (ppm): 1.78(6H, m); 2.82(2H, m); 4.14(2H, m); 4.47(3H, m); 6.03(1H, d); 6.79(1H, d); 7.46(3H, m); 7.77(2H, m).

Through biological assays the anti-inflammatory and analgesic activity were determined, for instance of nitric esters (IA) having the following formulae:



The anti-inflammatory activity of said nitric esters of derivatives of propionic acid was determined in Wistar rats utilizing the method of carrageenan edema, as reported in C.A. WINTER, E. RISLEY, G.W. NUSS, Proc. Soc. Exp. Biol. Med. 111,544-547 (1962), while the

analgesic activity of said derivatives was determined in Swiss mice as reported by L.C. HENDERSHOT, J. FORSAITH, J.Pharmacol. Exp. Ter. 125,237-249 (1959).

5 The anti-inflammatory and analgesic activity of said derivatives resulted to be comparable to 2-(6-methoxy-2-naphtyl)propionic acid taken as a reference.

10 The anti-platelet aggregation activity of said derivatives was determined on human platelets. Platelets were incubated with the compounds for 10 min at 37°C prior to stimulation with trombin. The anti-platelet aggregation activity of said derivatives resulted to be comparable to 2-( 6-methoxy-2 -naphthyl)propionic acid taken as a reference.

15 Then, the acute toxicity of said derivatives (IV) and (V) was evaluated by oral administration of a single dose of each composition (IV) and (V), utilizing groups of 10 Swiss mice for each derivative.

20 The incidence of lethality and the onset of a toxic symptomatology were reported for an observation period of 14 days.

Even after the administration of a dose of 750 mg/kg of composition (IV) or composition (V) no apparent toxicity symptoms were observed in the treated animals.

25 Further biological assays were carried out in order to define the pharmaco-toxicological profile of the studied compounds, in particular of composition (V),

compared with 2-(6-methoxy-2-naphtyl)propionic acid taken as reference.

#### A. PHARMACODYNAMIC ACTIVITY

##### ACUTE MODELS

5 Rat carrageenan paw edema. On the basis of preliminary experiments, the compound (V) and 2-(6-methoxy-2-naphtyl)propionic acid prove to have a comparable efficacy; the effective dose is comprised in the range from 1 to 10 mg/kg p.o.

##### 10 SUBACUTE MODELS

Rat adjuvant arthritis. The animals treated for 19 running days (from the 3rd to the 20th day after the inducing injection) with composition (V) or with 2-(6-methoxy-2-naphtyl)propionic acid, both of them at doses of 3 mg/kg p.o., showed a significant and comparable reduction in arthritic symptomatology compared with controls.

#### B. GASTROINTESTINAL TOLERABILITY

Damage to the gastric mucosa of the rat. The compound (V) was studied in comparison with 2-(6-methoxy-2-naphtyl)propionic acid taken as reference, both of them at doses comprised between 3 and 30 mg/kg p.o.; the compound (V) proved to be significantly better tolerated than 2-(6-methoxy-2-naphtyl)propionic acid. 2-(6-methoxy-2-naphtyl)propionic acid already at 3 mg/kg caused gastric damages, and such effects resulted to be dose-dependent, while the compound (V) proved to be

well tolerated even at doses of 30 mg/kg.

#### C. GENERAL PHARMACOLOGY

A secondary pharmacological evaluation of compound (V) was carried out in comparison with 2-(6-methoxy-2-naphtyl)propionic acid. No considerable additional effects with respect to the primary pharmacological activity were observed on central nervous system, on the autonomous system, on the cardiovascular, respiratory and gastrointestinal systems.

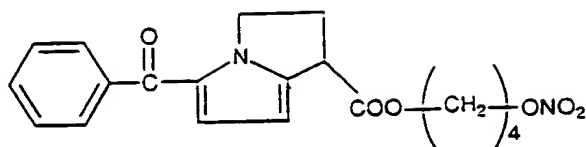
#### D. TOXICOLOGY

Acute toxicity in rodents. Preliminary studies were carried out in rodents, utilizing two administration routes. No symptoms of apparent toxicity were observed in animals treated with oral or intraperitoneal doses of 300 mg/kg.

Maximum tolerated dose in non-rodents. Preliminary studies have indicated that compound (V) was very well tolerated in the dog, an animal species which is known to be particularly sensitive to the ulcerogenic activity of anti-inflammatory agents in general. The animals received increasing oral doses of compound (V) up to 30 mg/kg and no apparent symptoms were observed. In comparison, 2-(6-methoxy-2-naphtyl)propionic acid, administered at doses of 10 mg/kg, caused the death of the animals.

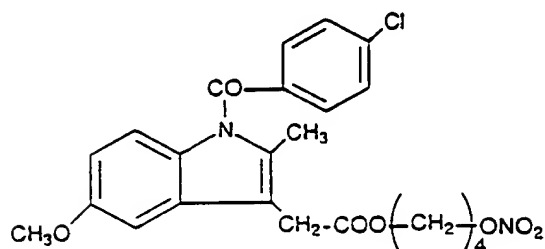
Furthermore, biological studies concerning nitric esters (IA) having the following formulae:





(XXXIV)

5



(XXXVI)

10

were carried out.

Then the anti-inflammatory activity, the gastrointestinal tolerability and the platelet anti-aggregating activity of the above compositions were determined.

15

The anti-inflammatory activity was determined by the method of the carrageenan edema in the rat, as described by C.A.WINTER et al. (1962) Proc.Soc.Exp.Biol.Med. 111,544. The gastrointestinal tolerability was evaluated by oral administration in the rat. The platelet anti-aggregating activity was determined on human platelets stimulated by arachidonic acid, according to the method described by V.BERTELE et al. (1983) Science 220, 517.

20

The results are shown on Table 1 as values concerning the anti-inflammatory, anti-aggregating activity and the gastrointestinal tolerability of the compositions

25

under examination, expressed as a power ratio relatively to the basic product taken as a unity standard.

TABLE 1

5	COMPOSITION	ANTI-INFLAMM.	ANTI-AGGREG.	GASTROINTEST.
		ACTIVITY	ACTIVITY	ULCEROGEN.
	(XXXIV)	1,25	1,10	0,15
	KETOROLAC	1,0	1,0	1,0
	(XXXVI)	1,0	1,30	0,1
	INDOMETHACIN	1,0	1,0	1,0

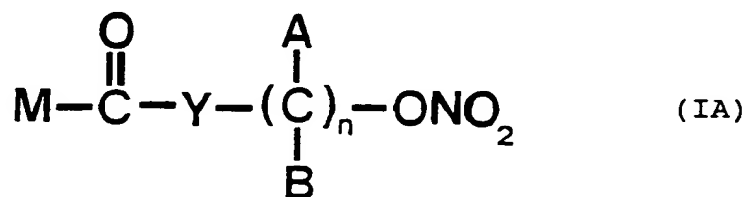
10 The acute toxicity of the compositions under examination has been approximately evaluated by oral administration of a single dosage of the substance to groups of 10 mice. The death-rate incidence and the onset of toxic symptoms have been observed for a period of 14  
15 days. Even after the administration of 100 mg/kg of each composition, the animals did not show any symptom of apparent toxicity.

20

25

## CLAIMS

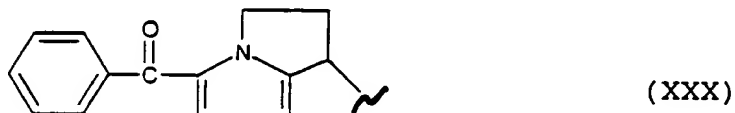
1. Derivatives of propionic acid, 1-(p-chlorobenzoyl)  
-5- methoxy-2-methyl -3-indolylacetic acid, 5-benzoyl  
-1,2-dihydro -3H- pyrrolo[1,2-a]pyrrole -1-carboxylic  
5 acid, 6-methoxy -2-naphthylacetic acid, characterized  
in that they have the following general formula:



10

where:

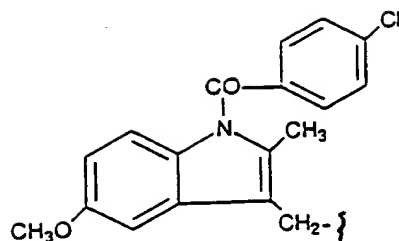
- A and B are chosen among hydrogen, linear or branched,  
substituted or non substituted alkyl chains, M is  
15 chosen among:



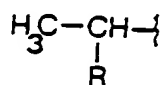
20



25

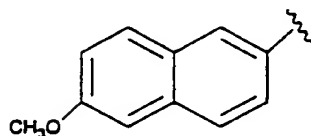


(XXXII)

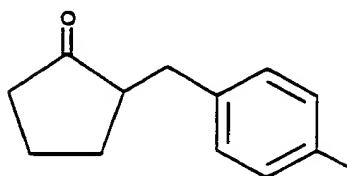


(XXXIII)

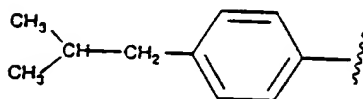
where R is chosen among:



(II)



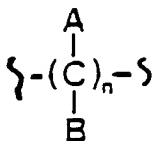
(X)



(III)

Y is chosen among oxygen, NH, NR<sub>1</sub>, where R<sub>1</sub> is a linear or branched alkyl group, and n is comprised between 1 and 10.

2. Nitric esters according to claim 1, characterized in that the fragment:

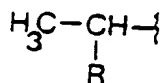


5

is a linear, branched or cyclic alkylenic group  $\text{C}_2\text{-C}_{10}$ .

3. Derivative of propionic acid according to claim 1, characterized in that M is equal to

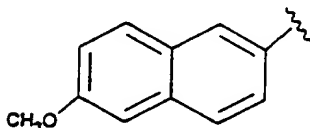
10



(XXXIII)

where R is:

15

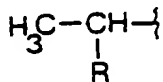


(II)

A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

20

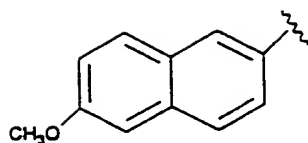
4. Derivative of propionic acid according to claim 1, characterized in that M is equal to



(XXXIII)

25

where R is:

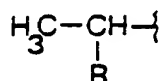


(II)

5

A and B are equal to hydrogen, Y is equal to NH, and n is equal to four.

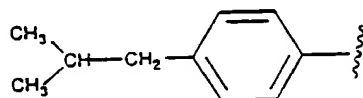
5. Derivatives of propionic acid according to claim 1,  
10 characterized in that M is equal to



(XXXIII)

15

where R is equal to:



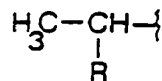
(III)

20

Y is equal to oxygen, A and B are equal to hydrogen, and n is equal to four.

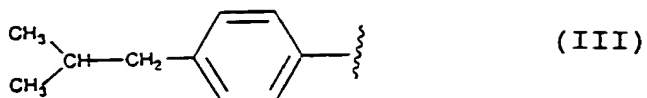
6. Derivative of propionic acid according to claim 1,  
25 characterized in that M is equal to

25



(XXXIII)

where R is equal to:



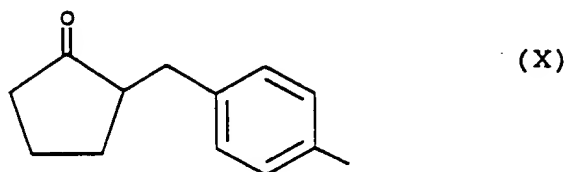
5

Y is equal to NH, A and B are equal to hydrogen, and n is equal to four.

7. Derivative of propionic acid, according to claim 1,  
10 characterized in that M is equal to



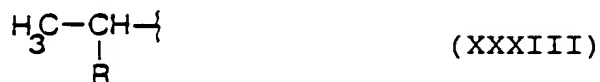
15 where R is equal to



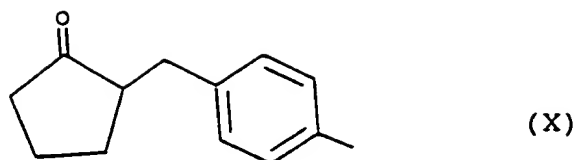
20 A and B are equal to hydrogen, y is equal to oxygen and n is equal to four.

8. Derivative of propionic acid according to claim 1,  
characterized in that M is equal to

25



where R is equal to

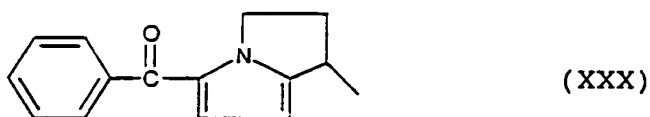


5

A and B are equal to hydrogen, y is equal to NH and n is equal to four.

9. Derivatives of 5-benzoyl -1,2-dihydro-3H-pyrrolo[1,2-a] pyrrole -1-carboxylic acid according to claim 1, characterized in that M is equal to

10

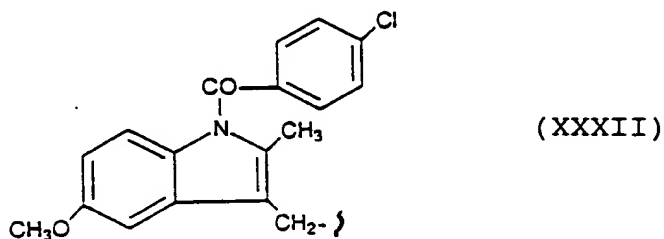


15

A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

10. Derivatives of 1-(p- chlorobenzoyl) -5-methoxy - 2-methyl-3-indolylacetic acid according to claim 1, characterized in that M is equal to

20



25

A and B are equal to hydrogen, Y is equal to oxygen and



n is equal to four.

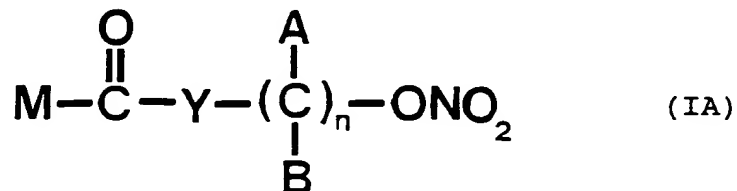
11. Nitric esters according to claim 1, characterized in that they are utilizable in the pharmaceutical field as anti-inflammatory agents.

5 12. Nitric esters according to claim 1, characterized in that they are utilizable in the pharmaceutical field as analgesic agents.

13. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.

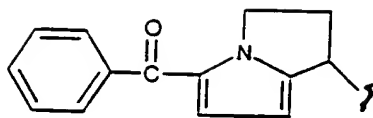
14. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of the diseases of the cardiovascular system, in the treatment of senile dementia, in the treatment of miocardial and brain ischemiae and in cases of arterial thrombosis.

15. Process for the preparation of nitric esters according to claim 1 and having the following general formula:



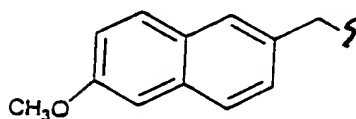
25 where A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains,

M is chosen among



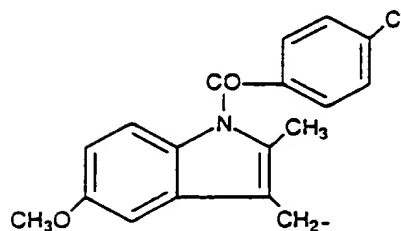
(XXX)

5



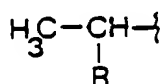
(XXXI)

10



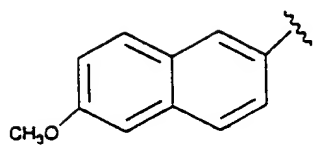
(XXXII)

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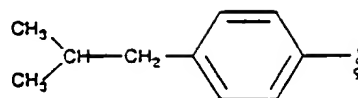
(XXXIII)

20 where R is chosen among:



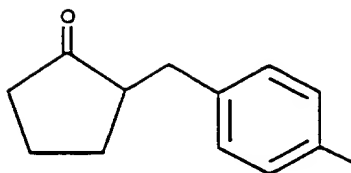
(II)

25



(III)

36



(X)

5

Y is chosen among oxygen, NH, NR<sub>1</sub>, where R<sub>1</sub> is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

- 10 - Preparation of sodium salt of derivatives having the following general formula:



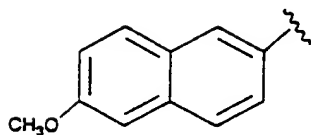
15

where M is chosen among (XXX), (XXXI), (XXXII),

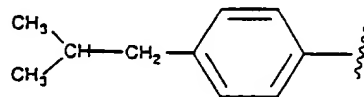


- 20 where R is chosen among the following structures:

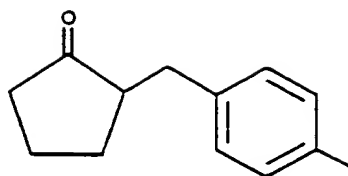
25



(II)



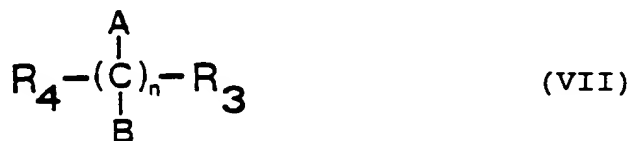
(III)



(X)

or preparation of derivatives (VIA) functionalized to the carboxylic group, such as acyclic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a compound having the following general formula:

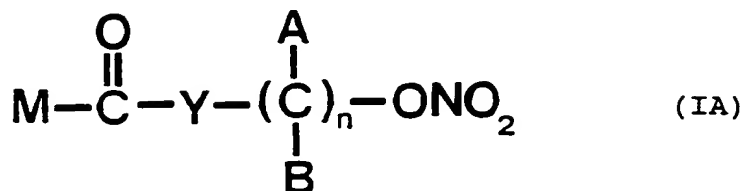


where:

$R_4$  is chosen among chlorine, bromine,  $NHR_5$  with  $R_5$  hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains,  $R_3$  is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

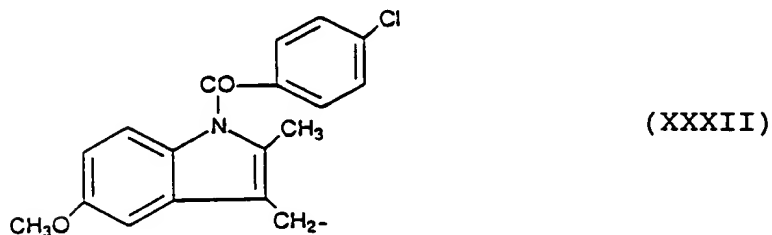
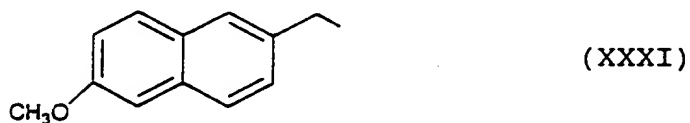
- Reaction of said monomeric esters or said amides with a nitrating agent such as  $AgNO_3$  or the like, with ensuing production of nitric esters (IA).

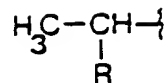
16. Process for the preparation of nitric esters according to claim 1 and having the following general formula:



where:

10 A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, M is chosen among

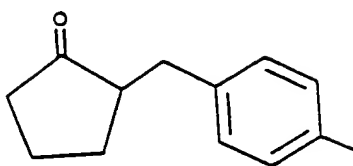




(XXXIII)

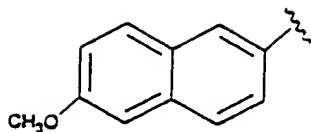
5

where R is chosen among:



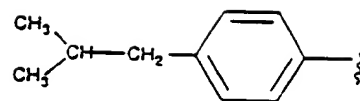
(X)

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(II)

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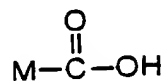


(III)

Y is chosen among oxygen, NH, NR<sub>1</sub>, where R<sub>1</sub> is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

20

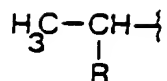
- Preparation of sodium salt of derivatives having the following general formula:



(VIA)

25

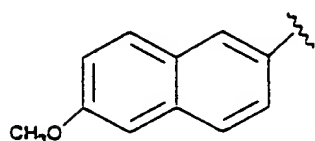
where M is chosen among (XXX), (XXXI), (XXXII),



(XXXIII)

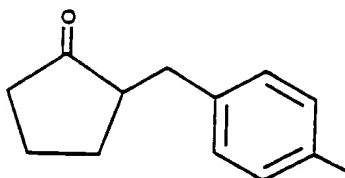
5

where R is chosen among the following structures:



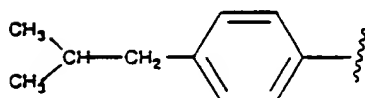
(II)

10



(X)

15



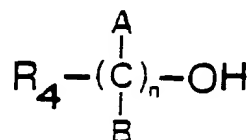
(III)

or preparation of derivatives (VIA) functionalized to the carboxylic group, such as acyclic chlorides, anhydrides or the like;

20

- Reaction between the sodium salt of said derivatives (VIA) or of said derivatives (VIA) functionalized to the carboxylic group, with a composition having the following general formula:

25



(VIII)

where:

$R_4$  is chosen among chlorine, bromine,  $NHR_5$  with  $R_5$  hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with an halogenating compound such as  $PBr_3$  or the like, with ensuing production of said monomeric esters or said amides, characterized by the presence of a terminal halogen group;

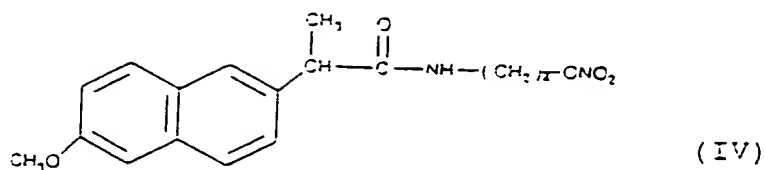
- Reaction of said monomeric esters or of said amides, characterized by the presence of a terminal halogen group with a nitrating agent such as  $AgNO_3$  or the like, with ensuing production of nitric esters (IA).

17. Pharmaceutical compositions having anti-inflammatory activity characterized in that they comprise at least one nitric ester according to claim 1 as active constituent.

18. Pharmaceutical compositions having analgesic activity characterized in that they comprise at least one nitric ester according to claim 1 as active constituent.



Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



which is prepared as described in the following example, that is given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

#### EXAMPLE 2

a) 23.9 g of potassium-phthalimide dispersed into 200 ml of anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

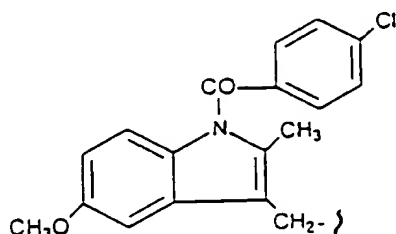
The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by <sup>1.33 KPa</sup> distillation at the pressure of ~~of~~ (10 mm Hg.)

The residue was regained with water and extracted with methylene chloride.

AMENDED SHEET  
IPEA/EP

n is equal to four.

10. Derivatives of 1-(p- chlorobenzoyl) -5-methoxy - 2-methyl-3-indolylacetic acid according to claim 1, characterized in that M is equal to



(XXXII)

A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

The use of  
11. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~ in the pharmaceutical field as anti-inflammatory agents.

The use of  
12. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~ in the pharmaceutical field as analgesic agents.

The use of  
13. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~ in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.

The use of  
14. ✓ Nitric esters according to claim 1, ~~characterized in that they are utilisable~~ in the treatment of the diseases of the cardiovascular system, in the treatment

PB - 53508

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Yes ☐ No ☒ → go to 6

(day month year)

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number (if known)	Filing date (day, month, year)

- 7 The answer must be NO if:
- any applicant is not an inventor
  - there is an inventor who is not an applicant, or
  - any applicant is a corporate body.

8 Please supply duplicates of claim(s), abstract, description and drawing(s).

Please mark correct box(es)

- 9 You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

Please sign here ➡

A completed fee sheet should preferably accompany the fee.

## INVENTORSHIP

- 7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes ☐

No ☒

A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

## Checklist

- 8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77

-

Claim(s)

10

Description

23

Abstract

1

Drawing(s)

-

- 8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

-

Translation(s) of Priority documents (please state how many)

-

Patents Form 7/77 – Statement of Inventorship and Right to Grant (please state how many)

-

Patents Form 9/77 – Preliminary Examination/Search

X

Patents Form 10/77 – Request for Substantive Examination

-

## Request

I/We request the grant of a patent on the basis of this application.

Signed

Date 6th October 1993  
(day month year)

LLOYD WISE, TREGEAR & CO.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

☐ The Comptroller  
The Patent Office  
State House  
66–71 High Holborn  
London  
WC1R 4TP

## OBJECT OF THE INVENTION

present invention refers to nitric esters of derivatives of propionic acid, their pharmaceutical utilization and the process for their preparation.

## PRIOR ART

Some derivatives of propionic acid, such as, for instance, 2-(6-methoxy-2-naphtyl)propionic acid, 2-(4-isobutylphenyl)propionic acid or alpha-Methyl-4-[(2-oxocyclopentyl)methyl]benzeneacetic acid, have been used for a long time in the pharmaceutical field for their anti-inflammatory activity and have been present for many years on the different world markets. The process for the preparation of 2-(6-methoxy-2-naphtyl)propionic acid has been described in the South African Patent N°6707,597, in the German Patent N° 1,934,460, corresponding to the US Patent N°3,637,767 and also in C.A.71,91162j (1969); HARRISON et al. J.Med.Chem. 13,203 (1970); the process for the preparation of 2-(4-isobutylphenyl)propionic acid has been described in Patents GB N°971,700, US N°3,228,831 and US N°3,385,886, and also in T. SHIORI, N. KAWAI, J.Org. Chem. 43,2936 (1978); J.T. PINHEY, B.A. ROWE, Tetrahedron Letters 21, 965 (1980); while the process for the preparation of alpha-methyl-4-[(2-oxocyclopentyl)methyl]benzenacetic acid has been described in the German

Patent N°2,814,556 and in US Patent N°4,161,538.

In the case of 2-(6-methoxy-2-naphtyl)propionic acid, the pharmacological profile is described in ROSZKOWSKI et al. J. Pharmacol. Exp. Ther. 179,114 (1971), while the pharmacological profile of 2-(4-isobutylphenyl)propionic acid is reported in ADAMS et al. Arch. Pharmacodyn. Ther. 178,115 (1969).

The utilization of these derivatives of propionic acid as anti-inflammatory agents involves, as known, extremely severe adverse reactions affecting, for instance, the gastrointestinal system, as well as damages to liver and kidneys. There are many experimental evidences [S. MONCADA, R.M.J. PALMER, E.A. HIGGS, Pharmacological Reviews, 43 (2), 109-142 (1991); T.F. LUSHER, C.M. BOULANGER, Y. DOHI, Z. YANG, Hypertension, 19,117-130 (1992)], on which basis the integrity of vasal endothelium is assumed to constitute a basic protection barrier against the onset of pathological processes in different organs and systems.

Such protection barrier, and therefore the integrity of vasal endothelium, is ensured on the physiological plane, by the presence of nitric oxide and prostacyclin.

The treatment with non steroidal drugs having an anti-inflammatory activity, such as, for instance, 2-(6-

methoxy-2-naphtyl)propionic acid or 2-(4-isobutylphenyl)propionic acid, causes the inhibition of cyclooxygenase, an enzyme which synthesizes the precursor of prostacyclin.

As a consequence, the production of prostacyclin being so inhibited, the tissue reserve of same is markedly depauperated and therefore the integrity of vasal endothelium is compromised.

As said, because of this endothelial damage due to the reduction of prostacyclin, diffuse pathological processes break out which affect the gastrointestinal system, the renal system and the liver.

Furthermore, as known, during inflammatory processes, new enzyme proteins, such as for example, nitric oxide synthetase, are induced; these enzyme proteins are partially responsible for the supporting of the inflammation [T.I.P.S. 14,287(1993)].

#### OBJECTS OF THE INVENTION

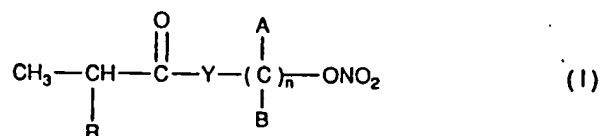
Object of the present invention is that of providing a product which, while assuring at least the maintenance of the pharmacological activity which is characteristic of the known anti-inflammatory agents, is capable of eliminating the adverse reactions brought about by the treatment with said agents.

Another object of the present invention is that of

realizing a process for the preparation of derivatives of propionic acid having an anti-inflammatory activity and exempt from the adverse reactions that are typical of anti-inflammatory agents.

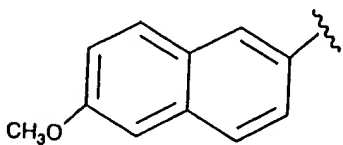
#### DESCRIPTION OF THE INVENTION

These and still further objects and associated advantages which shall clearly result from the following description, are reached by derivatives of propionic acid which, according to the present invention, have the following general formula:

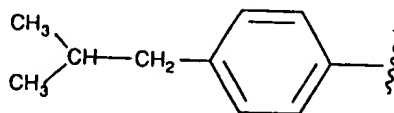


where:

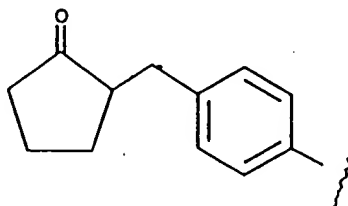
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, while R is chosen among:



(II)



(III)



(X)



is chosen among oxygen, NH,  $\text{NR}_1$ , where  $\text{R}_1$  is a linear or branched alkyl group, and n is comprised between 1 and 10.

In fact, it has been observed that the introduction of a group such as a terminal nitric ester in the derivatives of propionic acid as in (I) permits to maintain the pharmacological activity which is characteristic of anti-inflammatory non steroidal agents, while eliminating the adverse reactions caused by the treatment with such drugs. Furthermore, the introduction of a terminal nitric ester in the derivatives of propionic acid as in (I), permits to potentiate the anti-inflammatory effect compared with the well known non-steroidal anti-inflammatory drugs; such increase is made by the terminal nitric ester group, which can be considered as a source of nitric oxide and which can exert additional anti-inflammatory effects.

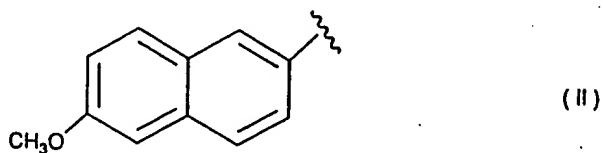
It has been also observed that the derivatives (I) are useful in the treatment of different unhealthy conditions, such as, for instance, rheumatic diseases in general, disorders of an immunologic nature, and they can also alleviate moderate-medium painful states of any kind.

Moreover, the derivatives (I) subject matter of this

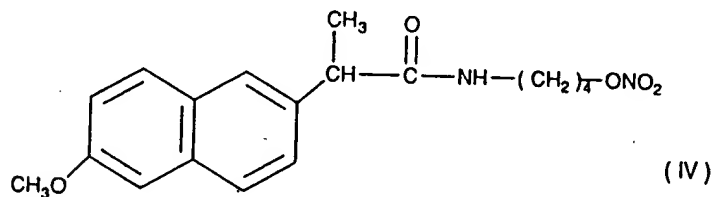
invention, are useful in the treatment of the illnesses of the cardiovascular system, and in particular in the treatment of myocardial and brain ischemiae, as well as in some cases of arterial thrombosis.

Always according to this invention, a nitric ester of a derivative of propionic acid (I) proved to be particularly advantageous, where:

hydrogen is chosen as A and B, as R is chosen:

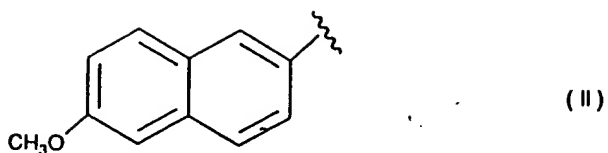


NH is chosen as Y, and n is equal to four, according to the following formula:

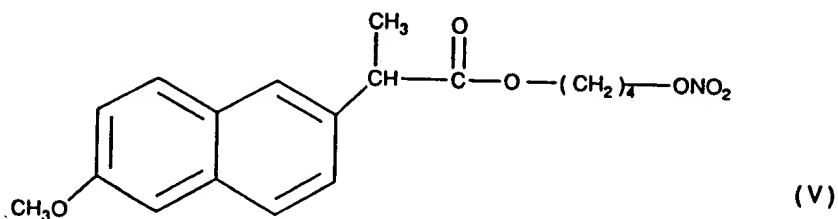


A nitric ester of a derivative of propionic acid (I) has also proved to be particularly advantageous according to this invention, where:

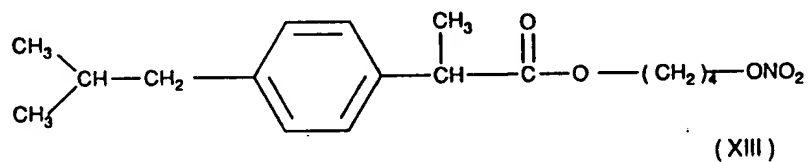
hydrogen is chosen as A and B, as R is chosen:



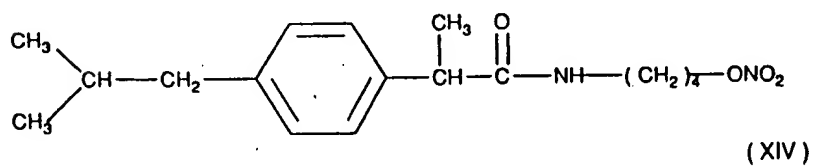
oxygen is chosen as Y, an n is equal to four, according to the following formula:



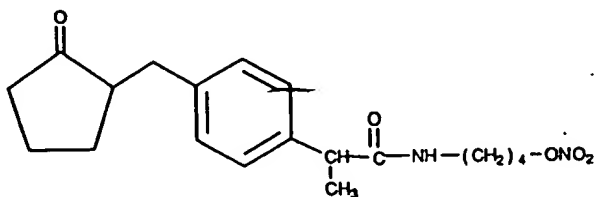
Also the nitric esters of derivatives of 2-(4-isobutylphenyl)propionic acid have proved to be particularly advantageous according to this invention, having the following formulae:



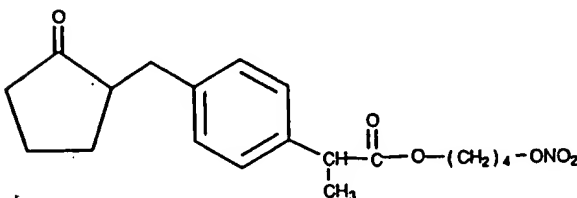
and



Always according to the present invention, nitric esters of derivatives of propionic acid (I) have proved to be particularly advantageous, having the following formulae:



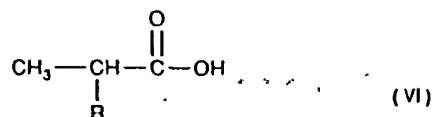
(XI)



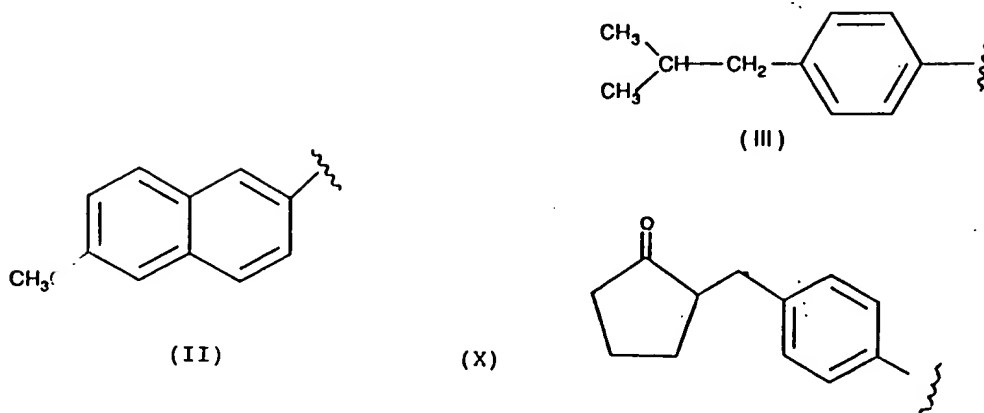
(XII)

For the preparation of nitric esters of derivatives (I) of propionic acid subject matter of the present invention, a first process has proved to be particularly advantageous which, according to the present invention, includes the following steps:

- Preparation of sodium salt of derivatives of propionic acid having the following general formula:

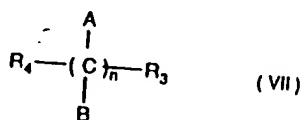


where R is chosen among the following structures:



or preparation of derivatives (VI) of propionic acid functionalized to the carboxylic group as acyclic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VI) of propionic acid or of said derivatives (VI) of propionic acid functionalized to the carboxylic group, with a composition having the following general formula:



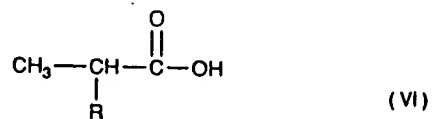
where:

$R_4$  is chosen among chlorine, bromine,  $NHR$  with  $R$  hydrogen, linear or branched alkyl chain,  $A$  and  $B$  are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains,  $R_3$  is chosen among chlorine, bromine and iodine, and  $n$  is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

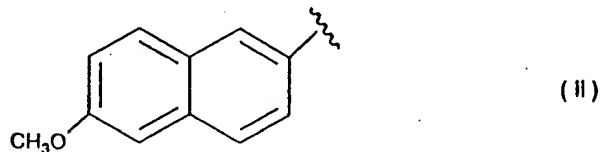
- Reaction of said monomeric esters or said amides with a nitrating agent such as  $AgNO_3$  or the like, with ensuing production of nitric esters or derivatives of propionic acid (I).

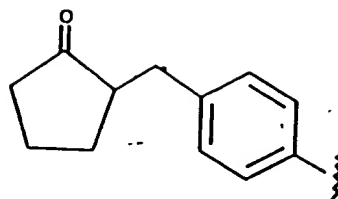
A second process has also proved to be particularly advantageous which, always according to the present invention, includes the following steps:

- Preparation of sodium salt of derivatives of propionic acid having the following general formula:

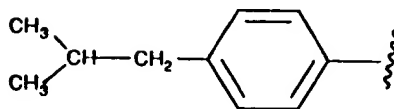


where  $R$  is chosen among the following structures:





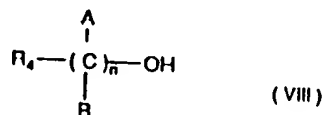
(X)



(III)

or preparation of derivatives (VI) of propionic acid functionalized to the carboxylic group, such as acyclic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VI) of propionic acid or of said derivatives (VI) of propionic acid functionalized to the carboxylic group, with a composition having the following general formula:



where;

$\text{R}_4$  is chosen among chlorine, bromine, NHR with R hydrogen, linear or branched alkyl chains, A and B are

chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with an halogenating composition such as  $\text{PBr}_3$  or the like, with ensuing production of said monomeric esters or said amides characterized by the presence of a terminal halogen group;

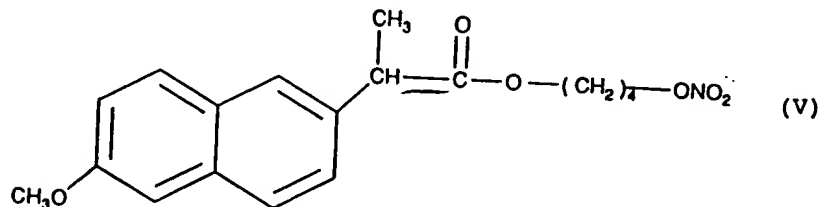
- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group, with a nitrating agent such as  $\text{AgNO}_3$  or the like, with ensuing production of nitric esters or derivatives of propionic acid (I).

The solvents which are utilized in the processes subject matter of the present invention are preferably chosen among chloroform, methylene chloride, acetonitrile, dimethylformamide, tetrahydrofuran, 1,4-dioxane and the like.

Such processes for the preparation of derivatives of propionic acid (I), subject matter of the present invention, consist of a limited number of steps, which permits to obtain in a short time the products which derive from these processes, with satisfactory yields and in high amounts, also on the industrial level.



According to the processes subject matter of this invention, the preparation of a nitric ester derived from propionic acid has proved to be particularly advantageous, having the following formula:



which is prepared as described in the example that is given hereunder as a mere indication and which does not limit in any way the protection scope of the invention.

#### EXAMPLE 1

a) 0.59 g of EtONa dissolved in 10 ml of ethyl alcohol were added, by slow dripping, to a solution of 2 g of 2-(6-methoxy-2-naphthyl)propionic acid, dissolved in 20 ml of ethyl alcohol. The reaction mixture was stirred for 5 minutes at room temperature, then the solvent was evaporated at a reduced pressure, obtaining 2.1 g of sodium salt of 2-(6-methoxy-2-naphthyl)propionic acid. The 2.1 g of sodium salt of 2-(6-methoxy-2-naphthyl)propionic acid so obtained were dispersed in 40 ml of dimethylformamide and 1.5 g of 1-Br-4-Cl-butane dissol-

ved in 30 ml of dimethylformamide were added by dripping to this dispersion. The reaction mixture was stirred for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The organic phase so extracted was anhydriified on sodium sulfate and the solvent was evaporated at a reduced pressure until a dry residue of 2 g was obtained.

The residue was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v).

The head fractions were collected, the solvent was evaporated at a reduced pressure and 1 g of 2-(6-methoxy-2-naphtyl)propionate of 4-chlorobutyl (IX) was obtained.

IR( $\text{cm}^{-1}$ ): C=O, 1669.

$^1\text{H-NMR}$ (300MHz) ( $\text{CDCl}_3$ ): 1.6ppm (d, 3H); 1.75ppm (m, 4H); 3.45ppm (m, 2H); 3.88ppm (q, 1H); 3.91ppm (1, 3H); 4.1ppm (m, 2H); 7.1-7-7.7ppm (m, aromatics).

Mass spectrometry (i.e.):  $\text{M}^+$  320.

b) 0.79 g of  $\text{AgNO}_3$  dissolved in 1.3 ml of acetonitrile were dripped to 1 g of (IX) obtained as described in a), dissolved in 4,5 ml of acetonitrile. The reaction mixture was stirred for 12 hours at a temperature of  $85^\circ\text{C}$  and then filtered.

From the resulting solution, the solvent was evaporated

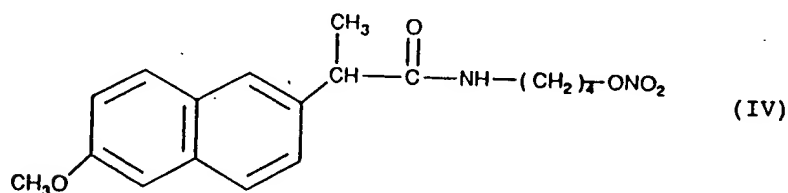
at a reduced pressure, and a residue was obtained to which 10 ml of methylene chloride were added. The mixture so obtained was filtered once again, the organic phase was washed with water and then anhydriified on sodium sulfate. The solvent was evaporated under reduced pressure and 1.8 g of a dry residue was obtained, which was purified by chromatography on silica gel, utilizing an eluting mixture constituted by hexane/ether 7/3 (v/v). The fractions containing the product were collected, the solvent was evaporated at a reduced pressure and 1.5 g of nitric ester of 2-(6-methoxy-2-naphthyl)propionate of 4-hydroxy-butyl (V) were obtained.

IR( $\text{cm}^{-1}$ ): C=O, 1733;  $\text{ONO}_2$ , 1637.

$^1\text{H-NMR}$ (300MHz) ( $\text{CDCl}_3$ ): 1.6ppm (d, 3H); 1.65ppm (m, 4H); 3.8ppm (q, 1H); 3.9ppm (s, 3H); 4.1ppm (m, 2H); 4.3ppm (m, 2H); 7.1-7.7ppm (m, aromatics).

Mass spectrometry (i.e.)  $\text{M}^+$  347.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester derivated from propionic acid proved to be particularly advantageous, having the following formula:



which is prepared as described in the following example, that is given hereunder as a mere indication and which does not limit in any way the protection scope of this invention.

EXAMPLE 2

a) 23.9 g of potassium-phthalimide dispersed into 200 ml of anhydrous dimethylformamide were added to a solution of 55.7 g of 1,4-di bromo-butane dissolved in 300 ml of anhydrous dimethylformamide.

The reaction mixture was agitated for 12 hours at room temperature, then diluted with water and extracted with methylene chloride. The methylene chloride was evaporated from the organic phase so obtained at a reduced pressure and then the dimethylformamide was removed by distillation at the pressure of 10 mm Hg.

The residue was regained with water and extracted with methylene chloride.

The organic phase so obtained was anhydriified and the solvent was evaporated at a reduced pressure until 14.8 g of 1-phthalimide-4-bromo-butane were obtained, which were treated with isopropyl ether and then essiccated.

m.p. = 77°C

b) 32 ml of hydriodic acid were cautiously added to 8.25 g of 1-phthalimido-4-bromo-butane; the mixture was then submitted to heating and kept in ebullition for 24

hours.

ter cooling, the mixture was diluted with water and after filtration the solvent was evaporated at a reduced pressure, obtaining a residue which, once crystallized by ethyl ether, produced 6 g of 4-iodine-butylammonium iodide.

m.p. = 103°C

c) 7 ml of thionyl chloride were cautiously added to a solution of 2.3 g of 2-(6-methoxy-2-naphtyl)propionic acid in 15 ml of anhydrous chloroform. The reaction mixture was stirred for 40 minutes at room temperature and then the solvent was evaporated at a reduced pressure, obtaining 2.23 g of 2-(6-methoxy-2-naphtyl)propionylchloride.

2.3 g of 2-(6-methoxy-2-naphtyl)propionylchloride were dissolved in pyridine and the solution was cooled at the temperature of 0°C.

3.27 g of 4-iodobutylammonium iodide were added to this solution and the mixture so obtained was agitated for 1 hour at 0°C and then diluted with water and extracted with methylene chloride.

The organic phase so obtained was washed initially with a 10% solution of hydrochloric acid and afterward with a saturated solution of sodium bicarbonate, then the solvent was evaporated at a reduced pressure, obtaining

3.2 g of a dry residue. The residue was purified by chromatography on silica gel, utilizing methylene chloride as eluent.

The intermediate fractions were collected, the solvent was evaporated at a reduced pressure and 1.6 g of 2-(6-methoxy-2-naphtyl)-4-iodobutyl propionamide (XX) were obtained.

IR ( $\text{cm}^{-1}$ ): NH, 3294; C=O, 1651.

$^1\text{H-NMR}$ (300MHz) ( $\text{CDCl}_3$ ): 1.1-1.75 ppm (m, 4H);

1.6ppm (d, 3H); 3.1ppm (t, 2H); 3.2ppm (q, 2H); 3.7ppm (q, 1H); 3.9ppm (s, 3H); 5.35ppm (m, NH); 7.1-7.75ppm (m, aromatics).

d) A suspension of 1.6 g of 2-(6-methoxy-2-naphtyl)-4-iodobutyl propionamide in 20 ml of acetonitrile was heated at a temperature of about 40°C and stirred until a solution was obtained to which 1.0 g of  $\text{AgNO}_3$  were added.

The mixture was stirred for 1 hour at room temperature, then filtered and the solvent was evaporated at a reduced pressure. The residue obtained was regained with methylene chloride, the resulting mixture was filtered and the solvent was evaporated at a reduced pressure, and 0.8 g of dry residue were obtained which were purified by chromatography on silica gel, utilizing an eluting mixture constituted by methylene chlo-

ride/ethyl acetate 9/1 (v/v).

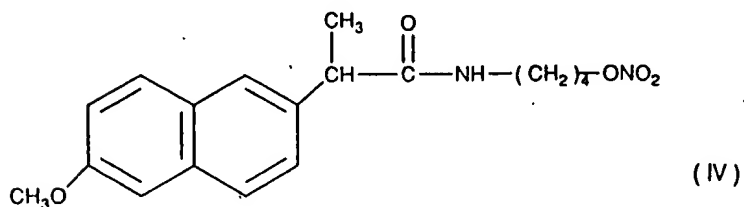
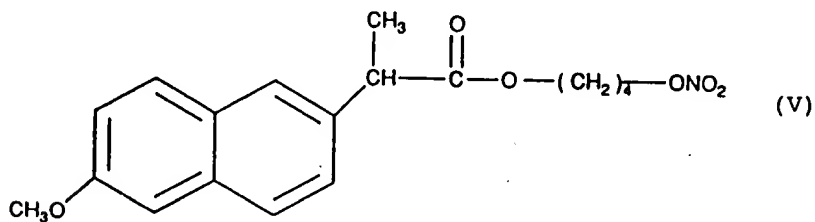
As head fractions were collected, the solvent was evaporated at a reduced pressure and 0.75 g of nitric ester of 2-(6-methoxy-2-naphthyl)-4-hydroxybutyl propionamide (IV) were obtained.

IR( $\text{cm}^{-1}$ ): C=O, 1672; NH, 3294;  $\text{ONO}_2$ , 1637

Mass spectrometry (i.e.)  $\text{M}^+$  346.

$^1\text{H-NMR}$ (80mhz) ( $\text{CDCl}_3$ ): 1.3ppm-1.6ppm (m, 4H); 1.7ppm (d, 3H); 3.1ppm (q, 2H); 3.7ppm (q, 1H); 3.9ppm (s, 3H); 4.3ppm (m, 2H); 5.6ppm (m, NH); 7.05-7.8ppm (m, aromatics).

Through biological assays the anti-inflammatory and analgesic activity were determined, for instance of nitric esters of derivatives of propionic acid (I) having the following formulae:



The anti-inflammatory activity of said nitric esters of derivatives of propionic acid was determined in Wistar rats utilizing the method of carrageenan edema, as reported in C.A. WINTER, E. RISLEY, G.W. NUSS, Proc. Soc. Exp. Biol. Med. 111,544-547 (1962), while the analgesic activity of said derivatives was determined in Swiss mice as reported by L.C. HENDERSHOT, J. FORSAITH, J.Pharmacol. Exp. Ther. 125,237-249 (1959).

The anti-inflammatory and analgesic activity of said derivatives resulted to be comparable to 2-(6-methoxy-2-naphtyl)propionic acid taken as a reference.

Then, the acute toxicity of said derivatives (IV) and (V) was evaluated by oral administration of a single dose of each composition (IV) and (V), utilizing groups of 10 Swiss mice for each derivative.

The incidence of lethality and the onset of a toxic symptomatology were reported for an observation period of 14 days.

Even after the administration of a dose of 750 mg/kg of composition (IV) or composition (V) no apparent toxicity symptoms were observed in the treated animals.

Further biological assays were carried out in order to define the pharmaco-toxicological profile of the stu-



died compounds, in particular of composition (V),  
pared with 2-(6-methoxy-2-naphtyl)propionic acid  
taken as reference.

#### A. PHARMACODYNAMIC ACTIVITY

##### ACUTE MODELS

Rat carrageenan paw edema. On the basis of preliminary experiments, the compound (V) and 2-(6-methoxy-2-naphtyl)propionic acid prove to have a comparable efficacy; the effective dose is comprised in the range from 1 to 10 mg/kg p.o.

##### SUBACUTE MODELS

Rat adjuvant arthritis. The animals treated for 19 running days (from the 3rd to the 20th day after the inducing injection) with composition (V) or with 2-(6-methoxy-2-naphtyl)propionic acid, both of them at doses of 3 mg/kg p.o., showed a significant and comparable reduction in arthritic symptomatology compared with controls.

#### B. GASTROINTESTINAL TOLERABILITY

Damage to the gastric mucosa of the rat. The compound (V) was studied in comparison with 2-(6-methoxy-2-naphtyl)propionic acid taken as reference, both of them at doses comprised between 3 and 30 mg/kg p.o.; the compound (V) proved to be significantly better tolerated than 2-(6-methoxy-2-naphtyl)propionic acid. 2-(6-

methoxy-2-naphtyl)propionic acid already at 3 mg/kg caused gastric damages, and such effects resulted to be dose-dependent, while the compound (V) proved to be well tolerated even at doses of 30 mg/kg.

#### C. GENERAL PHARMACOLOGY

A secondary pharmacological evaluation of compound (V) was carried out in comparison with 2-(6-methoxy-2-naphtyl)propionic acid. No considerable additional effects with respect to the primary pharmacological activity were observed on central nervous system, on the autonomous system, on the cardiovascular, respiratory and gastrointestinal systems.

#### D. TOXICOLOGY

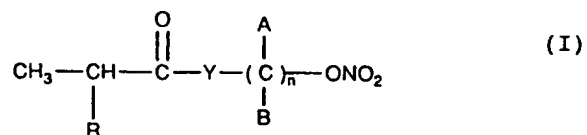
Acute toxicity in rodents. Preliminary studies were carried out in rodents, utilizing two administration routes. No symptoms of apparent toxicity were observed in animals treated with oral or intraperitoneal doses of 300 mg/kg.

Maximum tolerated dose in non-rodents. Preliminary studies have indicated that compound (V) was very well tolerated in the dog, an animal species which is known to be particularly sensitive to the ulcerogenic activity of anti-inflammatory agents in general. The animals received increasing oral doses of compound (V) up to 30 mg/kg and no apparent symptoms were observed. In compa-

risin, 2-(6-methoxy-2-naphthyl)propionic acid, administered at doses of 10 mg/kg, caused the death of the animals.

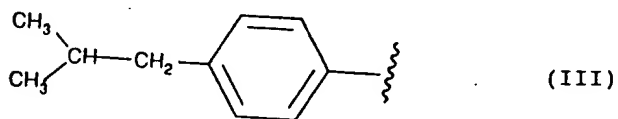
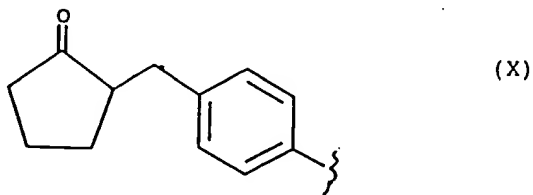
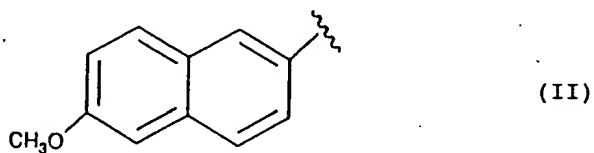
# CLAIMS

1. Derivatives of propionic acid characterized in that they have the following general formula:



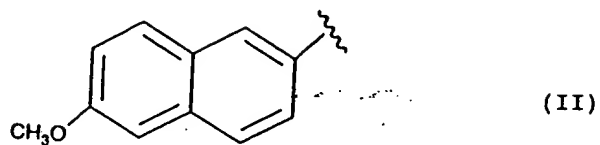
where:

A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:



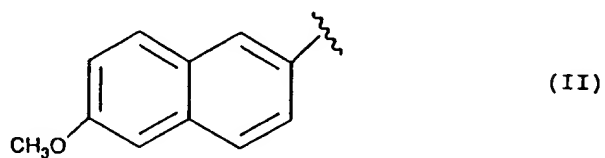
Y is chosen among oxygen, NH, NR<sub>1</sub>, where R<sub>1</sub> is a linear or branched alkyl group, and n is comprised between 1 and 10.

Derivative of propionic acid according to claim 1,  
 characterized in that R is:



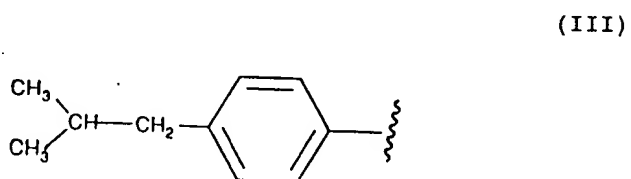
A and B are equal to hydrogen, Y is equal to oxygen,  
 and n is equal to four.

3. Derivative of propionic acid according to claim 1,  
 characterized in that R is:



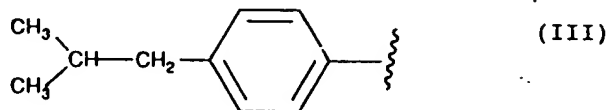
A and B are equal to hydrogen, Y is equal to NH, and n  
 is equal to four.

4. Derivatives of propionic acid according to claim 1,  
 characterized in that R is equal to:



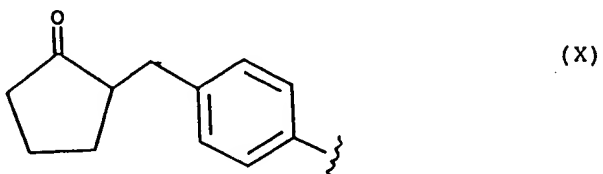
Y is equal to oxygen, A and B are equal to hydrogen, and n is equal to four.

5. Derivative of propionic acid according to claim 1, characterized in that R is equal to:



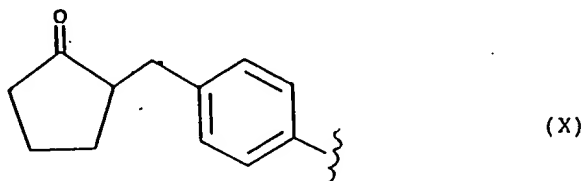
Y is equal to NH, A and B are equal to hydrogen, and n is equal to four.

6. Derivative of propionic acid, according to claim 1, characterized in that R is equal to



A and B are equal to hydrogen, y is equal to oxygen and n is equal to four.

7. Derivative of propionic acid according to claim 1, characterized in that R is equal to



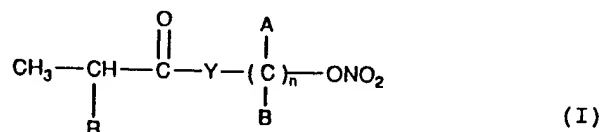
and B are equal to hydrogen, y is equal to NH and n is equal to four.

8. Derivatives of propionic acid according to claim 1, characterized in that they are utilizable in the pharmaceutical field as anti-inflammatory agents.

9. Derivatives of propionic acid according to claim 1, characterized in that they are utilizable in the treatment of rheumatic illnesses, in the treatment of disorders of an immunologic nature and of the moderate to medium painful states.

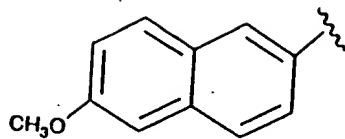
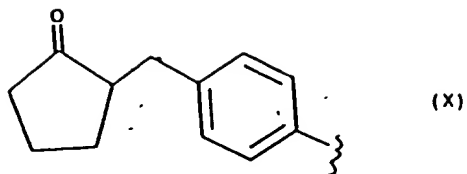
10. Derivatives of propionic acid according to claim 1, characterized in that they are utilizable in the treatment of the diseases of the cardiovascular system, in the treatment of miocardial and brain ischemiae and in cases of arterial thrombosis.

11. Process for the preparation of derivatives of propionic acid according to claim 1 and having the following general formula:

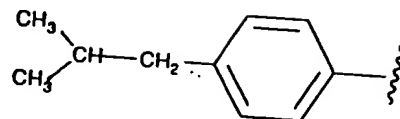


where A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains,

R is chosen among:



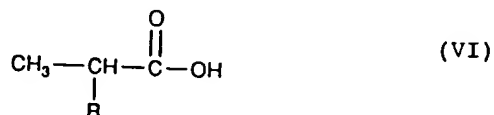
(II)



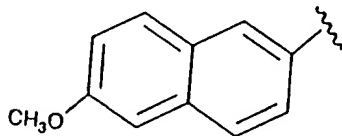
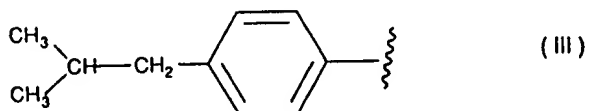
(III)

Y is chosen among oxygen, NH, NR<sub>1</sub>, where R<sub>1</sub> is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives of propionic acid having the following general formula:

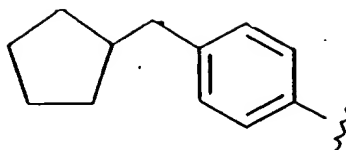


where R is chosen among the following structures:



(II)

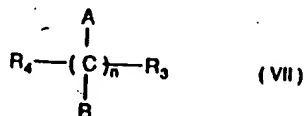




(X)

or preparation of derivatives (VI) of propionic acid functionalized to the carboxylic group, such as acyclic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VI) of propionic acid or of said derivatives (VI) of propionic acid functionalized to the carboxylic group, with a compound having the following general formula:



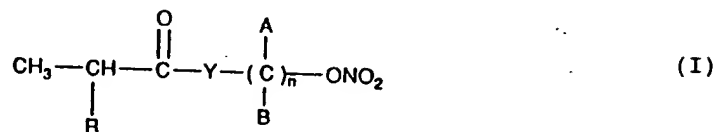
where:

$\text{R}_4$  is chosen among chlorine, bromine,  $\text{NHR}$  with  $\text{R}$  hydrogen, linear or branched alkyl chain,  $\text{A}$  and  $\text{B}$  are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains,  $\text{R}_3$  is chosen among chlorine, bromine and iodine, and  $n$  is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as  $\text{AgNO}_3$  or the like, with

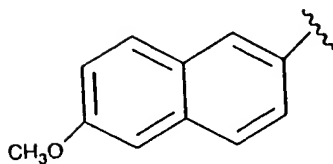
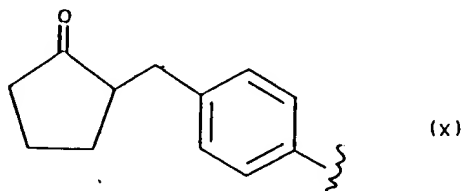
ensuing production of nitric esters of derivatives of propionic acid (I).

12. Process for the preparation of derivatives of propionic acid according to claim 1 and having the following general formula:

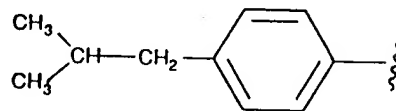


where:

A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:



(II)

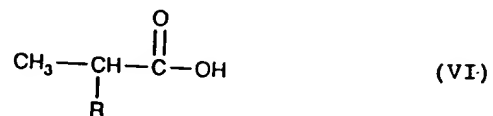


(III)

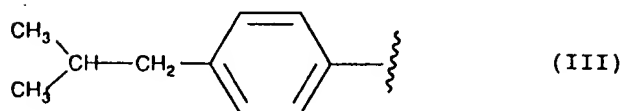
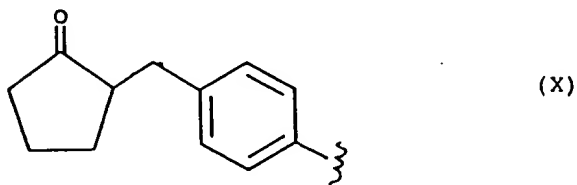
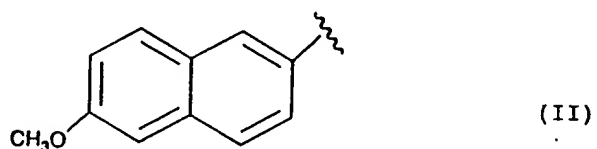
Y is chosen among oxygen, NH, NR<sub>1</sub>, where R<sub>1</sub> is a linear or branched alkyl group, and n is comprised between 1

and 10, characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives of propionic acid having the following general formula:



where R is chosen among the following structures:



or preparation of derivatives (VI) of propionic acid functionalized to the carboxylic group, such as acyclic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (VI) of propionic acid or of said derivatives (VI) of

propionic acid functionalized to the carboxylic group, with a composition having the following general formula:



where:

$\text{R}_4$  is chosen among chlorine, bromine,  $\text{NHR}$  with  $\text{R}$  hydrogen, linear or branched alkyl chain,  $\text{A}$  and  $\text{B}$  are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and  $n$  is comprised between 1 and 10, with ensuing production of the relevant monomeric esters or the relevant amides;

- Reaction of said monomeric esters or said amides with an halogenating compound such as  $\text{PBr}_3$  or the like, with ensuing production of said monomeric esters or said amides, characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or of said amides, characterized by the presence of a terminal halogen group with a nitrating agent such as  $\text{AgNO}_3$  or the like, with ensuing production of nitric esters or derivatives of propionic acid (I).

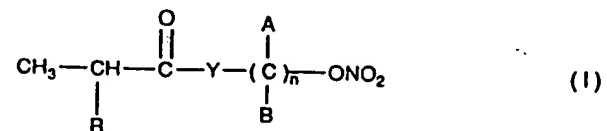
13. A derivative of propionic acid as claimed in Claim 1 substantially as herein described with reference to the Example.

14. A process as claimed in Claim 11 substantially as herein described with reference to the Example.

ABSTRACT

NITRIC ESTERS OF DERIVATIVES OF PROPIONIC ACID AND  
PROCESS FOR THEIR PREPARATION.

The present invention refers to nitric esters of derivatives of propionic acid having the following general formula:



their pharmaceutical use and the process for their preparation.